A framework for the assessment and management of post-traumatic symptomatology in the aftermath of critical illness through music and sound interventions

by

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Abstract

Background: Post-intensive care syndrome (PICS) is a major long-term complication of critical illness for both patients and their families, causing significant loss of function and worsening quality of life. Therefore, early detection and treatment of PICS morbidities is required to minimize long-term sequelae, reduce the rate of re-hospitalization, and optimize functional recovery. To date, there is no unified approach to either assessment or management of PICS. Moreover, despite the effectiveness of music interventions for the improvement of outcomes in the ICU, so such interventions have been tested for PICS.

Aim: This thesis aims to delineate a framework for the assessment and management of post-traumatic symptomatology after critical illness through music and sound interventions. Specific objectives included to a) Summarize neurobiological evidence on th e pathophysiology of PTSD and the areas of the brain involved, as well as some of the effects of music on PTSD and ICU survivors to highlight potential mechanisms and effects of music on individuals suffering from post-ICU PTSD. b) Identify existing tools for screening of PTSD and PICS in ICU survivors and their families, and to examine evidence on the validity, reliability, and feasibility of existing tools, as reflected in published peer-reviewed studies.

Methods: The first phase employed a critical narrative review to elucidate an evidence-based neurobiological framework to inform the study of music interventions for PTSD post-ICU. This review was directed by methodological recommendations by Ferrari and the Scale for the Assessment of Narrative Review Articles guided reporting. The second phase employed scoping review methodology to synthesize evidence on tools assessing PTSD and PICS in ICU survivors

and their families. The review was directed by a protocol based on current guidance for scoping reviews and reporting was guided by Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

Results: Key structures in PTSD symptomatology include: the prefrontal cortex, the amygdalae, and the hippocampus. A dysfunctional HPA axis feedback loop, an increased amygdalic response, hippocampal atrophy, and a hypoactive prefrontal cortex contribute to PTSD symptoms. Playing or listening to music can stimulate neurogenesis and neuroplasticity, enhance brain recovery, and normalize stress response. Additionally, evidence supports the effectiveness of music to improve coping and emotional regulation, decrease dissociation symptoms, reduce depression and anxiety levels, and overall reduce severity of PTSD symptoms. However, no studies on music interventions post-ICU were identified. The scoping review revealed a) a limited number of tools addressing all 3 domains of PICS, b) unclear validity of the tools in the post-ICU population, especially for the recommended time-frame of assessment at 2-4 weeks post-discharge, c) limitations with some tools' feasibility in the post-ICU population, d) low diagnostic accuracy of cognitive assessment tools, e) evidence of appropriate psychometric properties and feasibility of psychological health assessment tools, and g) only two tools addressing PICS in families of ICU survivors.

Conclusion and Implications: Overall, this thesis highlights important considerations for future research in the development of assessment tools for PICS, as well as music as a potential approach to manage post-traumatic symptomatology in ICU survivors.

Keywords: ICU survivors, Post Intensive care Syndrome, Family caregivers, screening tools, psychometric properties, Music, Post traumatic stress disorder, critical illness, neurobiology

Table of Contents

Background

Evidence suggests that ICU survivors often suffer substantial long-term complications of the critical illness and ICU stay (Desai et al., 2011; Geense et.al., 2021; Needham et al., 2012; Rawal et al., 2017; Rousseau et al., 2021). These include the consequences of prolonged immobility, altered cognition and development of neuropsychiatric symptoms, which can affect socioeconomic status and quality of life after critical illness (Needham et al., 2012). These can be more pronounced in survivors already experiencing social deprivation (Bastian et al., 2018), and thus can be very devastating (Annachiara et al., 2018; Davidson et al., 2013; Needham et al., 2012; Parker et al., 2015; Wintermann et al., 2015). This constellation of sequelae is described under the umbrella term Post Intensive Care Syndrome (PICS). PICS may commonly transition to chronic impairments, thus increasing the risk for mortality and morbidity in ICU survivors (Needham et al., 2012; Rawal et al., 2017). PICS not only affects ICU survivors, but also their families and dramatically increases costs for healthcare systems (Ruhl et al., 2015).

Post-intensive Care Syndrome

PICS is defined as a new or worsening impairment in 3 domains: a) physical such as ICU-acquired neuromuscular weakness, b) cognitive such as memory, attention, and executive function, or c) psychological such as anxiety, depression, or PTSD, arising after critical illness and persisting beyond discharge from acute care hospitalization (Geense et al., 202; Needham et al., 2012; Rousseau et al., 2021). More than 64% of ICU survivors with no pre-existing cognitive impairment and disability exhibit one or more symptoms of PICS at 3 months and 49% at 1-year post discharge (Annachiara et al., 2018). Moreover, co-occurrence of PICS symptoms from two or more domains is present in 21%-25%, while all domains of PICS symptoms are present in 4%-6% of ICU survivors (Annachiara et al., 2018). A major risk factor of PICS is ICU delirium and duration of

delirium (Amra et al., 2018). Other risk factors include high disease severity, ICU length of stay and duration of mechanical ventilation, hypoglycemia, hyperglycemia, hypoxemia, hypotension, older age, female sex, sedatives, previous mental health conditions and negative ICU experience (Desai et al., 2011; Geense et al., 2021; Lee et al., 2020).

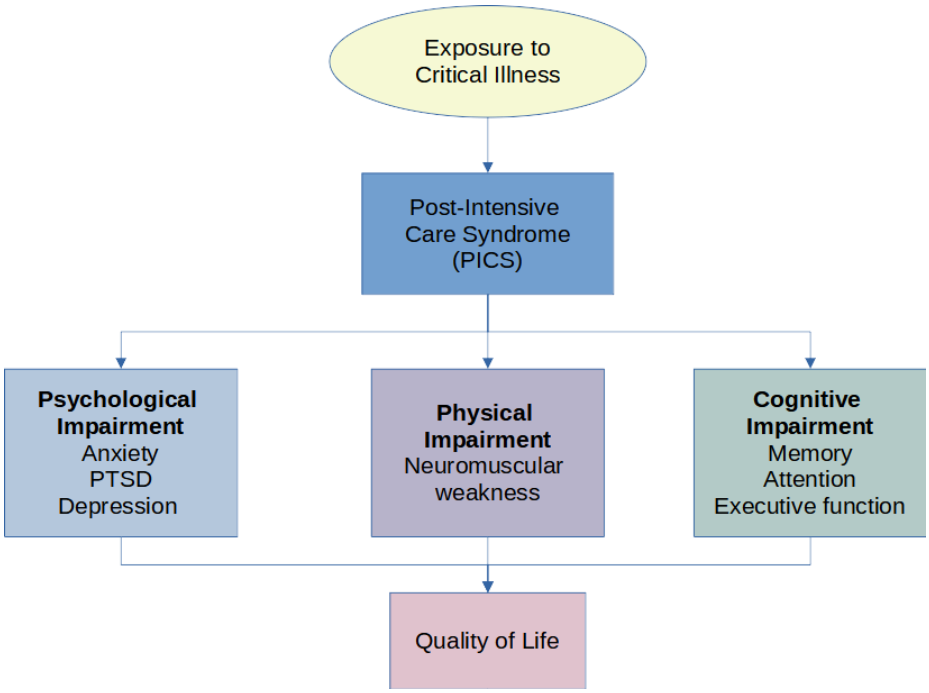

Figure 1. Components of post-Intensive Care Syndrome in ICU Survivors

Physical impairments

Intensive care unit muscle wasting is one of the factors that cause muscle weakness and physical disability in ICU survivors (Dinglas et al., 2017; Kress & Hall, 2014; Ohtake et al., 2018). It can be defined as the symmetric acute muscle weakness of the extremities. This is prevalent among 40% of ICU survivors (Appleton et al., 2015; Geense et al., 2021). The pathophysiology of intensive care unit acquired weakness includes microvascular ischemia and immobility that lead to skeletal muscle wasting. Furthermore, microvascular injury also results in nerve ischemia and dysfunction of sodium channels that contribute to critical illness-related neuropathy or myopathy (Kress & Hall, 2014). Major risk factors associated with the development of ICU-acquired

weakness include female sex, age, prolonged mechanical ventilation, sepsis, multisystem organ failure, prolonged period of bed-restore deep sedation (Geense et al., 2021; Lee et al., 2020; Needham et al., 2014).

Cognitive impairments

ICU survivors experience high prevalence of cognitive impairment: 40 % at hospital discharge (Chung et.al., 2017), 73 % at 3 months with no significant improvement even after 12 months (Estrup et.al., 2018). Cognitive impairments include impaired memory, executive function, language, attention, and visual–spatial abilities (Rengel et al., 2019). The exact pathophysiology of cognitive impairment in ICU survivors is unknown; however, it may be the manifestation of brain dysfunction during critical illness. The major risk factors associated with cognitive impairment are delirium in the ICU, acute brain dysfunction, hypoxia, hypotension, glucose dysregulation, respiratory failure requiring prolonged mechanical ventilation, sepsis, and age (Collet et al., 2021; Davydow et al., 2013; Lee et al., 2020; Mitchell et al., 2018).

Psychological impairment and PTSD

Depression, anxiety, and PTSD are major psychological morbidities following critical illness, which can persist from months to years (Desai et al., 2011). The risk of developing psychological difficulties after critical illness ranges from 1-62% (Desai et al., 2011; Pandharipande et al., 2013). PTSD is characterized by four important symptom domains: intrusive memories, hyper-arousal, avoidance and negative alterations in mood or cognition that develop following traumatic experiences in the ICU lasting more than 1 month and cause significant distress or changes in functionality (American Psychiatric Association, 2013). Point prevalence estimates of PTSD among ICU survivors are 15.93%, 16.80%, 18.96%, and 20.21% at 3, 6, 12, and > 12 months after discharge, respectively (Righy et al., 2019). Moreover, PTSD also influences

cognitive abilities such as memory and learning, and often causes social withdrawal. Thus, PTSD has a strong impact on the quality of life in ICU survivors, affecting it in intensely negative ways, including ability to work and study (Jackson et al., 2014). Clinically significant PTSD symptoms occur in 20% of ICU patients in the first 12 months post-ICU discharge and are associated with worse health related quality of life (Parker et al., 2015). Pre-existing psychopathology is the only pre-ICU factor associated with PTSD symptoms. Furthermore, ICU-related factors include sedation, delirium, early memories of frightening ICU experiences, severity of illness, ICU length of stay and mechanical ventilation (Amra et al., 2018; Lee et al., 2020; Parker et al., 2015).

These physical, psychological, and cognitive impairments have a major impact on the quality of life and socioeconomic status of ICU survivors. Available evidence suggests that around half of the ICU survivor population require caregiver assistance even after 1-year post discharge (Briegel et al., 2013). Nearly 30% of the ICU survivors do not go back to work, and another 30% do not go back to their pre-ICU job or salary at 1 year following ICU discharge (Griffiths et al., 2013). This ratio is even worse in case of ICU survivors with more than 4 days of mechanical ventilation during ICU stay; only 10% of them are independent and working at 1-year post discharge (Desai et al., 2011; Needham et al., 2012). Furthermore, 16.2% of ICU survivors are re-hospitalized within 30 days of discharge, and 18.9% between 31-180 days (Hua et al., 2015). Moreover, over one quarter of those re-hospitalizations involve ICU admission (Hua et al., 2015).

PICS and PTSD in Family Caregivers

Family caregivers are integral care partners throughout patients' trajectories of critical illness and recovery. Caregivers of both surviving and non-surviving ICU patients suffer a wide range of psychological, physical, cognitive, and social problems, which may persist for years, and are termed as Post Intensive Care Syndrome-Family (PICS-F) (Heyland et al., 2018; Needham et

al., 2012). Overall, 10-75% of ICU patients' family members show symptoms of anxiety persisting for years (Davidson et al., 2012). Moreover, 33% of family members may require serious medical assistance for anxiety or depression (Harvey & Davidson, 2016; Jezierska, 2014). Furthermore, 8-42% of families exhibit symptoms of PTSD, and this percentage becomes 50% in cases of patients' decedents or critically ill children (Davidson et al., 2012). In a study by Kentish-Barnes et. al., 52% of the families showed symptoms of complicated grief at 6 months (Kentish-Barnes et.al., 2015). Moreover, the risk of PTSD is high in family members who experience a patient's death in the ICU, or participated in end-of-life decision-making (Kross et al., 2011). The risk factors for PICS-F and PTSD include female sex, morbidity, younger relative and patient age, lower educational level, critically ill spouse, pre-existing psychological, unmarried parent of a critically ill child and history of anxiety, depression, or severe mental disease (Davidson et al., 2012; Harvey & Davidson, 2016).

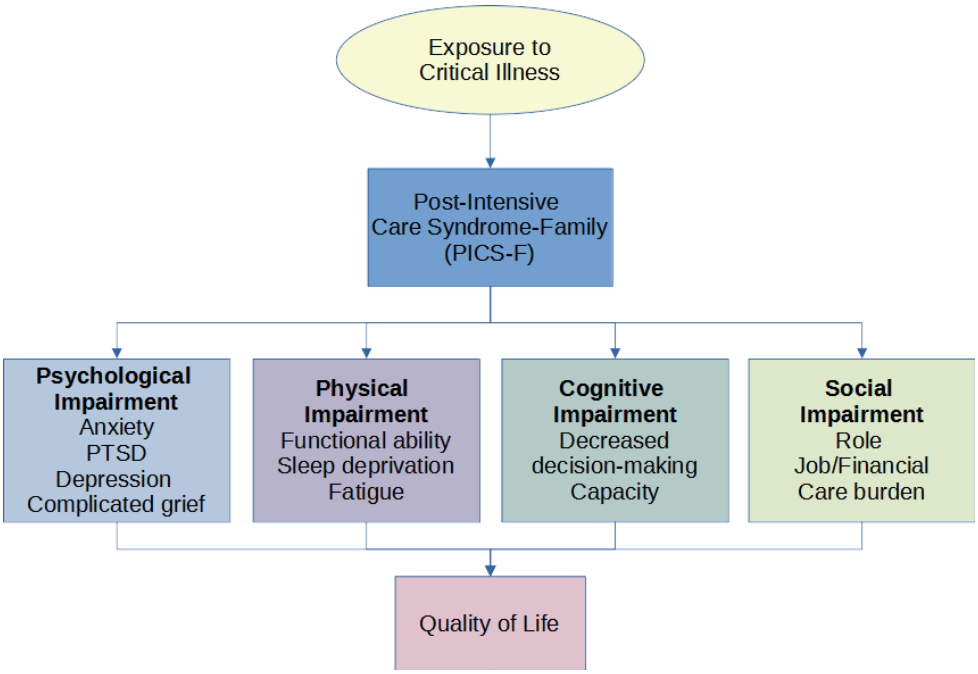

Figure 2. Post-Intensive Care Syndrome-Family

Beyond the psychological burden, financial stress is also common for families of ICU survivors (Kamdar et al., 2017). Evidence shows that nearly 50% of family members had to make some adjustments to their working life to accommodate their care-giving responsibilities 12 months after discharge (Day et al., 2013; Griffiths et al., 2013). Care giver strain is another aspect that impacts the quality of life of families of ICU patients, with 65% of caregivers experiencing difficulty sleeping during their family member's ICU stay due to anxiety and tension (Day et al., 2013). This disruption in quality of sleep is evident in 40% caregivers, even at 3 months after discharge from ICU (van den Born-van Zanten et al., 2016). Other major strains reported include family adjustments (51%) and changes in personal plans (42%) (van den Born-van Zanten et al., 2016).

Management of PICS and PTSD

A number of approaches to improve ICU related complications such as physical and cognitive rehabilitation have been tested with varied results (Fuke et al., 2018; Jackson et al., 2012). However, despite the high prevalence of psychological impairments following critical illness there is still no effective system in place to prospectively identify patients at risk, and to provide timely care after hospital discharge. Moreover, lack of timely and adequate treatment strategies for post-ICU psychological impairment leads to ED visits or readmission that further strain the health care system. Intensive care unit follow-up clinics are expected to be a place for follow-up and treatment of these psychological consequences developed during and after hospitalization. However, there is insufficient evidence regarding the usefulness of ICU follow-up clinics. Pharmacotherapy is one of the common treatment strategies for PTSD. But the positive effects of psychopharmacological interventions typically do not extend past the active treatment period (Williams et.al., 2022). Additionally, there is evidence that pharmaceutical treatment for

PTSD may not be clinically effective (Cukor et al., 2010). Drug therapies for PTSD have been most effective in decreasing hyperarousal and mood symptoms such as depression (Astill Wright et al., 2019), and less effective for the symptoms of re-experiencing, emotional numbing, and behavioral avoidance. Moreover, individual differences such as histories of side effects, response, and comorbidities also outweigh treatment-specific differences (Astill Wright et al., 2019).

Only a few approaches addressing survivors' and families' psychological well-being other than pharmacotherapy are available (Choi et al., 2016; Lasiter et al., 2016; Wade et al., 2016). There is evidence that intensive care unit diaries can help orientate the patient and prevent psychological impairment by alleviating anxiety and depression. A recent study investigating the effect of ICU diaries on posttraumatic stress disorder symptoms in ICU survivors and their relatives reported that ICU diaries may have a significant effect on patient's anxiety and depression, whereas, ineffective for PTSD (McIlroy et al., 2019). Moreover, evidence on the efficacy of intensive care unit diaries for families of ICU patients is inconclusive (Garrouste-Orgeas et al., 2019; Nielsen et al., 2020). Other interventions focusing on enhancing coping skills, such as family-centered support, family-clinician communication, and complex psychological interventions did not appear to significantly affect family members' burden of psychological symptoms (Bohart et al., 2018; Cox et al., 2018; Wade et al., 2019; White et al., 2018). Moreover, condolence letters were likewise found to have no impact on alleviating grief and in fact may have increased the prevalence or severity of depression and PTSD symptoms (Kentish-Barnes et al., 2017). In a study that assessed the feasibility and efficacy of implementing "Family Care Rituals" among family members of ICU patients with a high risk of mortality found family members' involvement in providing care to the patient in the ICU was associated with reduced symptoms of PTSD, but more research is required to draw conclusions (Amass et al., 2020). Cognitive

behavioral therapy (CBT) is a major intervention in the management of post-ICU PTSD. However, there are questions on the effectiveness of CBT after treatment stops. Moreover, all patients with PTSD do not respond well to CBT therapy and still retain significant symptoms of PTSD on discharge (Carr et al., 2012; Spinazzola et al., 2005). CBT is found ineffective in patients with prolonged and multiple exposures to trauma (Spinazzola et al., 2005), and poor verbal memory (Wild & Gur, 2008). These therapies also have been associated with high levels of attrition (21%) (Imel et al., 2013; Paintain and Cassidy, 2018). Thus, there is a need to explore and develop other forms of interventions for the treatment of PTSD in ICU survivors.

Need for Evidence Synthesis

Recently, research in the field of ICU-related PTSD and PICS have increased its emphasis on preventive and therapeutic approaches (Amra et al., 2018; Appleton et al., 2015; Jackson et al., 2012; Wade et al., 2016). Early identification and initiation of treatment have been shown to improve the patient outcomes (Lasiter et al., 2016; McIlroy et al., 2019; Wade et al., 2016). Thus, valid, and reliable screening tools are vital for early detection, as well as evaluation of the intervention outcomes. However, there is no gold standard tool or guidelines available for the assessment of ICU-related PTSD and PICS (American Psychological Association, 2017; Needham et al., 2012; Umberger, 2019). Lack of evidence on the comparative psychometric properties of the assessment tools is a major barrier in evidence-based screening. Systematic reviews on risk factors, incidence rates and interventions for psychiatric morbidity (PTSD and PICS) in ICU survivors as well as family are available, but so far, none of the reviews have evaluated or assessed the psychometric properties of assessment tools.

Although integrative interventions and music therapy during the acute ICU stay have received some attention, there is a paucity of studies exploring the effects of music post-ICU

admission. Few reviews have evaluated the effect of art therapy such as painting, song writing, and music on PTSD (Baker et al., 2018; Gooding & Langston, 2019). Evidence from various studies shows significant effects of individual and group music therapy in reduction of core PTSD symptoms and increase in social function among PTSD patients. Moreover, music therapy in adult psychiatric patients with persistent PTSD, who had been unable to benefit from CBT, showed a significant decrease of all dimensions of PTSD symptoms (Carr et al., 2012). Music guided relaxation has also shown a positive impact in reducing depression, PTSD and increasing sleep quality in veterans (Blanaru et al., 2012). A recent theoretical review of music and PTSD have shown the possibility of effectiveness of music on PTSD (Landis-Shack et al., 2017). However, more evidence is needed to speculate the neurobiology of post traumatic symptomatology and possibility of sound and music interventions to effectively treat post-ICU PTSD.

Therefore, this study aims to fill this gap by synthesizing evidence on the available assessment tools for PTSD and PICS in ICU survivors and family and summarize current evidence regarding the role of music for PTSD symptoms post-ICU.

Research Objectives

This thesis aims to inform approaches for the assessment and management of post-traumatic symptomatology in the aftermath of critical illness through music and sound interventions:

The study will evolve in 2 phases. Specific objectives for each phase include:

1) Phase I: Summarize neurobiological evidence on the pathophysiology of PTSD and the areas of the brain involved, as well as some of the effects of music on PTSD and ICU survivors to highlight potential mechanisms and effects of music on individuals suffering from post-ICU PTSD.

2) Phase II: Identify existing tools for screening of PTSD and PICS in ICU survivors and their families, and to examine evidence on the validity, reliability, and feasibility of existing tools, as reflected in published peer-reviewed studies.

Methods

The thesis followed a paper-based format. Two manuscripts were produced from the first and the second phase of the study. The first phase employed a scoping review methodology and the second phase followed narrative review methodology.

First Phase: Narrative review to delineate an evidence-based theoretical framework of the effects of music on PTSD post-ICU

Critical narrative reviews are useful at identifying and summarizing what has been previously published and pursuing new study areas not yet addressed. Its primary purpose is to reflect on the current knowledge gaps, highlight the significance of new research and speculate on new types of interventions available (Ferrari, 2015). The strength of critical review methodology is its ability to explore gaps and synthesize knowledge to propose innovation to existing theory. Critical narrative review methodology involves a "degree of analysis and conceptual innovation" which is required to achieve the objectives of the first phase of the proposed study (Baethge et al., 2019). Thus, we used a critical narrative review methodology as this was deemed most appropriate for the delineation of a theoretical framework on music effects on PTSD post-ICU**.** This review was directed by methodological recommendations by Ferrari (Ferrari, 2015) and the Scale for the Assessment of Narrative Review Articles (SANRA) guided reporting (Baethge et al., 2019).

Second Phase: Scoping review of PTSD/ PICS screening tools in ICU survivors and their families

Scoping reviews are useful for examining emerging evidence when it is still unclear what other, more specific questions can be posed and valuably addressed by a systematic review. Thus, the general purpose for conducting scoping reviews is to identify and map the available evidence. Moreover, scoping reviews are also used to identify knowledge gaps, scope a body of literature, clarify concepts, and investigate research conduct or to inform a systematic review (Colquhoun et al., 2014; Levac et al., 2010; Munn et al., 2018). The research question that guided the scoping review is "What are the properties, scope and uses of tools available for the assessment of PTSD and PICS in ICU survivors and their family or caregivers?" The review was directed by a protocol based on current guidance for scoping reviews (Levac et al., 2010). Reporting was guided by Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018).

References

Amass, T. H., Villa, G., OMahony, S., Badger, J. M., McFadden, R., Walsh, T., Caine, T., McGuirl, D., Palmisciano, A., Yeow, M. E., De Gaudio, R., Curtis, J. R., & Levy, M. M. (2020). Family Care Rituals in the ICU to Reduce Symptoms of Post-Traumatic Stress Disorder in Family Members-A Multicenter, Multinational, Before-and-After Intervention Trial. *Critical Care Medicine*, *48*(2), 176–184. https://doi.org/10.1097/CCM.0000000000004113

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

American Psychological Association. (2017). Clinical practice guideline for the treatment of posttraumatic stress disorder (PTSD) in adults. Retrieved from: *https://www.apa.org/ptsd-guideline*

Amra, S., John C., O., Mikhail, D., Dziadzko, V., Rashid, A., Tarun D., S., Rahul, K., Ann M., F., John D., F., Ronald, P., Ognjen, G., & Alejandro A., R. (2018). Potentially Modifiable Risk Factors for Long-Term Cognitive Impairment After Critical Illness: A Systematic Review. *Mayo Clinic Proceedings*, *93*(1), 68–82. https://doiorg/10.1016/j.mayocp.2017.11.005

Annachiara, M., Pratik P., P., Timothy D., G., Mayur B., P., Christopher G., H., James C., J., Jennifer L., T., Rameela, C., Eugene Wesley, E., & Nathan E., B. (2018). Co-Occurrence of Post-Intensive Care Syndrome Problems Among 406 Survivors of Critical Illness*. *Critical Care Medicine*, *46*(9), 1393–1401. https://doiorg/10.1097/CCM.0000000000003218

Appleton, R. T., Kinsella, J., & Quasim, T. (2015). The incidence of intensive care unit-acquired weakness syndromes: A systematic review. *Journal of the Intensive Care Society*, *16*(2), 126–136. https://doi.org/10.1177/1751143714563016

Astill Wright, L., Sijbrandij, M., Sinnerton, R., Lewis, C., Roberts, N. P., & Bisson, J. I. (2019). Pharmacological prevention and early treatment of post-traumatic stress disorder and acute stress disorder: a systematic review and meta-analysis. *Translational psychiatry*, *9*(1), 334. https://doi.org/10.1038/s41398-019-0673-5

Baethge, C., Goldbeck-Wood, S., & Mertens, S. (2019) SANRA-a scale for the quality assessment of narrative review articles. Research integrity and peer review, 4, 5. https://doi.org/10.1186/s41073-019-0064-8

Baker, F. A., Metcalf, O., Varker, T., & O'Donnell, M. (2018). A systematic review of the efficacy of creative arts therapies in the treatment of adults with PTSD. *Psychological Trauma: Theory, Research, Practice and Policy*, *10*(6), 643–651. https://doi.org/10.1037/tra0000353

Bastian, K., Hollinger, A., Mebazaa, A., Azoulay, E., Féliot, E., Chevreul, K., Fournier, M. C., Guidet, B., Michel, M., Montravers, P., Pili-Floury, S., Sonneville, R., Siegemund, M., Gayat, E., & FROG-ICU Study Investigators (2018). Association of social deprivation with 1-year outcome of ICU survivors: results from the FROG-ICU study. *Intensive care medicine*, *44*(12), 2025–2037. https://doi.org/10.1007/s00134-018-5412-5

Blanaru, M., Bloch, B., Vadas, L., Arnon, Z., Ziv, N., Kremer, I., & Haimov, I. (2012). The effects of music relaxation and muscle relaxation techniques on sleep quality and emotional measures among individuals with posttraumatic stress disorder. *Mental Illness*, *4*(2), e13. https://doi.org/10.4081/mi.2012.e13

Bohart, S., Egerod, I., Bestle, M. H., Overgaard, D., Christensen, D. F., & Jensen, J. F. (2018). Recovery programme for ICU survivors has no effect on relatives' quality of life: Secondary analysis of the RAPIT-study. *Intensive & critical care nursing*, *47*, 39–45. https://doi.org/10.1016/j.iccn.2018.03.002

Briegel, I., Dolch, M., Irlbeck, M., Hauer, D., Kaufmann, I., & Schelling, G. (2013). Ergebnisqualität der Therapie des akuten Lungenversagens : Veränderungen über einen Zeitraum von 2 Jahrzehnten [Quality of results of therapy of acute respiratory failure : changes over a period of two decades]. *Der Anaesthesist*, *62*(4), 261–270. https://doi.org/10.1007/s00101-013-2156-z

Carr, C., d'Ardenne, P., Sloboda, A., Scott, C., Wang, D., & Priebe, S. (2012). Group music therapy for patients with persistent post-traumatic stress disorder--an exploratory randomized controlled trial with mixed methods evaluation. *Psychology and Psychotherapy*, *85*(2), 179–202. https://doi.org/10.1111/j.2044-8341.2011.02026.x

Choi, J., Donahoe, MP., Hoffman, L.A., (2016). Psychological and physical health in family caregivers of intensive care unit survivors: current knowledge and future research strategies. *Journal of Korean Academy of Nursing*;46(2):159-167. http://dx.doi.org/10.4040/jkan.2016.46.2.159

Chung, C. R., Yoo, H. J., Park, J., & Ryu, S. (2017). Cognitive Impairment and Psychological Distress at Discharge from Intensive Care Unit. *Psychiatry investigation*, *14*(3), 376–379. https://doi.org/10.4306/pi.2017.14.3.376

Collet, M. O., Egerod, I., Thomsen, T., Wetterslev, J., Lange, T., Ebdrup, B. H., & Perner, A. (2021). Risk factors for long-term cognitive impairment in ICU survivors: A multicenter,

prospective cohort study. *Acta anaesthesiologica Scandinavica*, *65*(1), 92–99. https://doi.org/10.1111/aas.13692

Colquhoun, H. L., Levac, D., O'Brien, K. K., Straus, S., Tricco, A. C., Perrier, L., Kastner, M. & Moher, D. (2014). Scoping reviews: time for clarity in definition, methods, and reporting. *Journal of Clinical Epidemiology, 67*(12), 1291-1294. doi:10.1016/j.jclinepi.2014.03.013

Cox, C. E., Hough, C. L., Carson, S. S., White, D. B., Kahn, J. M., Olsen, M. K., Jones, D. M., Somers, T. J., Kelleher, S. A., & Porter, L. S. (2018). Effects of a Telephone- and Web-based Coping Skills Training Program Compared with an Education Program for Survivors of Critical Illness and Their Family Members. A Randomized Clinical Trial. *American Journal of Respiratory and Critical Care Medicine*, *197*(1), 66–78. https://doi.org/10.1164/rccm.201704-0720OC

Cukor, J., Olden, M., Lee, F., & Difede, J. (2010). Evidence-based treatments for PTSD, new directions, and special challenges. *Annals of the New York Academy of Sciences*, *1208*, 82–89. https://doi.org/10.1111/j.1749-6632.2010.05793.x

Davidson, J. E., Harvey, M. A., Schuller, J., & Black, G. (2013). Post-intensive care syndrome: What it is and how to help prevent it. *American Nurse Today*, *8*(5), 32-8.

Davidson, J. E., Jones, C., & Bienvenu, O. J. (2012). Family response to critical illness: postintensive care syndrome-family. *Critical Care Medicine*, *40*(2), 618–624. https://doi.org/10.1097/CCM.0b013e318236ebf9

Davydow, D. S., Zatzick, D., Hough, C. L., & Katon, W. J. (2013). In-hospital acute stress symptoms are associated with impairment in cognition 1 year after intensive care unit admission. *Annals of the American Thoracic Society*, *10*(5), 450–457. https://doi.org/10.1513/AnnalsATS.201303-060OC

Day, A., Haj-Bakri, S., Lubchansky, S., & Mehta, S. (2013). Sleep, anxiety and fatigue in family members of patients admitted to the intensive care unit: a questionnaire study. *Critical Care (London, England)*, *17*(3), R91. https://doi.org/10.1186/cc12736

Desai, S. V., Law, T. J., & Needham, D. M. (2011). Long-term complications of critical care. *Critical Care Medicine*, *39*(2), 371–379. https://doi.org/10.1097/CCM.0b013e3181fd66e5

Dinglas, V. D., Aronson Friedman, L., Colantuoni, E., Mendez-Tellez, P. A., Shanholtz, C. B., Ciesla, N. D., Pronovost, P. J., & Needham, D. M. (2017). Muscle Weakness and 5-Year Survival in Acute Respiratory Distress Syndrome Survivors. *Critical care medicine*, *45*(3), 446–453. https://doi.org/10.1097/CCM.0000000000002208

Estrup, S., Kjer, C., Vilhelmsen, F., Poulsen, L. M., Gøgenur, I., & Mathiesen, O. (2018). Cognitive Function 3 and 12 Months After ICU Discharge-A Prospective Cohort Study. *Critical care medicine*, *46*(12), e1121–e1127. https://doi.org/10.1097/CCM.0000000000003391

Ferrari, R. (2015) Writing narrative style literature reviews. Medical Writing, 24(4), 230-235. https://doi.org/10.1179/2047480615Z.000000000329

Fuke, R., Hifumi, T., Kondo, Y., Hatakeyama, J., Takei, T., Yamakawa, K., Inoue, S., & Nishida, O. (2018). Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: a systematic review and meta-analysis. *BMJ open*, *8*(5), e019998. https://doi.org/10.1136/bmjopen-2017-019998

Garrouste-Orgeas, M., Flahault, C., Vinatier, I., Rigaud, J. P., Thieulot-Rolin, N., Mercier, E., Rouget, A., Grand, H., Lesieur, O., Tamion, F., Hamidfar, R., Renault, A., Parmentier-Decrucq, E., Monseau, Y., Argaud, L., Bretonnière, C., Lautrette, A., Badié, J., Boulet, E., Floccard, B., … Timsit, J. F. (2019). Effect of an ICU Diary on Posttraumatic Stress

Disorder Symptoms Among Patients Receiving Mechanical Ventilation: A Randomized Clinical Trial. *JAMA*, *322*(3), 229–239. https://doi.org/10.1001/jama.2019.9058

Geense, W. W., Zegers, M., Peters, M., Ewalds, E., Simons, K. S., Vermeulen, H., van der Hoeven, J. G., & van den Boogaard, M. (2021). New Physical, Mental, and Cognitive Problems 1 Year after ICU Admission: A Prospective Multicenter Study. *American journal of respiratory and critical care medicine*, *203*(12), 1512–1521. https://doi.org/10.1164/rccm.202009-3381OC

Gooding, L. F., & Langston, D. G. (2019). Music Therapy With Military Populations: A Scoping Review. *Journal of Music Therapy*, *56*(4), 315–347. https://doi.org.login.ezproxy.library.ualberta.ca/10.1093/jmt/thz010

Griffiths, J., Hatch, R. A., Bishop, J., Morgan, K., Jenkinson, C., Cuthbertson, B. H., & Brett, S. J. (2013). An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. *Critical Care (London, England)*, *17*(3), R100. https://doi.org/10.1186/cc12745

Harvey, M. A., & Davidson, J. E. (2016). Postintensive Care Syndrome: Right Care, Right Now…and Later. *Critical Care Medicine*, *44*(2), 381–385. https://doi.org/10.1097/CCM.0000000000001531

Heyland, D. K., Davidson, J., Skrobik, Y., des Ordons, A. R., Van Scoy, L. J., Day, A. G., Vandall-Walker, V., & Marshall, A. P. (2018). Improving partnerships with family members of ICU patients: study protocol for a randomized controlled trial. *Trials*, *19*(1), 3. https://doi.org/10.1186/s13063-017-2379-4

Hua, M., Gong, M. N., Brady, J., & Wunsch, H. (2015). Early and late unplanned rehospitalizations for survivors of critical illness*. *Critical Care Medicine*, *43*(2), 430–438. https://doi.org/10.1097/CCM.0000000000000717

Imel Z. E., Laska K., Jakupcak M., Simpson T. L. (2013). Meta-analysis of dropout in treatments for posttraumatic stress disorder. *J. Consult. Clin. Psychol.* 81, 394–404. 10.1037/a0031474

Jackson, J. C., Ely, E. W., Morey, M. C., Anderson, V. M., Denne, L. B., Clune, J., Siebert, C. S., Archer, K. R., Torres, R., Janz, D., Schiro, E., Jones, J., Shintani, A. K., Levine, B., Pun, B. T., Thompson, J., Brummel, N. E., & Hoenig, H. (2012). Cognitive and physical rehabilitation of intensive care unit survivors: results of the RETURN randomized controlled pilot investigation. *Critical Care Medicine*, *40*(4), 1088–1097. https://doi.org/10.1097/CCM.0b013e3182373115

Jackson, J. C., Pandharipande, P. P., Girard, T. D., Brummel, N. E., Thompson, J. L., Hughes, C. G., Pun, B. T., Vasilevskis, E. E., Morandi, A., Shintani, A. K., Hopkins, R. O., Bernard, G. R., Dittus, R. S., Ely, E. W., & Bringing to light the Risk Factors and Incidence of Neuropsychological dysfunction in ICU survivors (BRAIN-ICU) study investigators (2014). Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. *The Lancet. Respiratory Medicine*, *2*(5), 369–379. https://doi.org/10.1016/S2213-2600(14)70051-7

Jezierska N. (2014). Psychological reactions in family members of patients hospitalised in intensive care units. *Anaesthesiology Intensive Therapy*, *46*(1), 42–45. https://doi.org/10.5603/AIT.2014.0009

Kamdar, B. B., Huang, M., Dinglas, V. D., Colantuoni, E., von Wachter, T. M., Hopkins, R. O., Needham, D. M., & National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network (2017). Joblessness and Lost Earnings after Acute Respiratory Distress Syndrome in a 1-Year National Multicenter Study. *American Journal of Respiratory and Critical Care Medicine*, *196*(8), 1012–1020. https://doi.org/10.1164/rccm.201611-2327OC.

Kentish-Barnes, N., Chaize, M., Seegers, V., Legriel, S., Cariou, A., Jaber, S., Lefrant, J. Y., Floccard, B., Renault, A., Vinatier, I., Mathonnet, A., Reuter, D., Guisset, O., Cohen-Solal, Z., Cracco, C., Seguin, A., Durand-Gasselin, J., Éon, B., Thirion, M., Rigaud, J. P., … Azoulay, É. (2015). Complicated grief after death of a relative in the intensive care unit. *The European respiratory journal*, *45*(5), 1341–1352. https://doi.org/10.1183/09031936.00160014

Kentish-Barnes, N., Chevret, S., Champigneulle, B., Thirion, M., Souppart, V., Gilbert, M., Lesieur, O., Renault, A., Garrouste-Orgeas, M., Argaud, L., Venot, M., Demoule, A., Guisset, O., Vinatier, I., Troché, G., Massot, J., Jaber, S., Bornstain, C., Gaday, V., Robert, R., Famirea Study Group (2017). Effect of a condolence letter on grief symptoms among relatives of patients who died in the ICU: a randomized clinical trial. *Intensive Care Medicine*, *43*(4), 473–484. https://doi.org/10.1007/s00134-016-4669-9

Kress, J. P., & Hall, J. B. (2014). ICU-acquired weakness and recovery from critical illness. *The New England Journal of Medicine*, *370*(17), 1626–1635. https://doi.org/10.1056/NEJMra1209390

Kross, E. K., Engelberg, R. A., Gries, C. J., Nielsen, E. L., Zatzick, D., & Curtis, J. R. (2011). ICU care associated with symptoms of depression and posttraumatic stress disorder among

family members of patients who die in the ICU. *Chest*, *139*(4), 795–801. https://doi.org/10.1378/chest.10-0652

Landis-Shack, N., Heinz, A. J., & Bonn-Miller, M. O. (2017). Music Therapy for Posttraumatic Stress in Adults: A Theoretical Review. *Psychomusicology*, *27*(4), 334–342. https://doi.org/10.1037/pmu0000192

Lasiter, S., Oles, S. K., Mundell, J., London, S., & Khan, B. (2016). Critical Care Follow-up Clinics: A Scoping Review of Interventions and Outcomes. *Clinical Nurse Specialist CNS*, *30*(4), 227–237. https://doi.org/10.1097/NUR.0000000000000219

Lee, M., Kang, J., & Jeong, Y. J. (2020). Risk factors for post-intensive care syndrome: A systematic review and meta-analysis. *Australian Critical Care*, *33*(3), 287–294 https://doi.org/10.1016/j.aucc.2019.10.004

Levac, D., Colquhoun, H., & O'Brien, K. K. (2010). Scoping studies: advancing the methodology. *Implementation Science: IS*, *5*, 69. https://doi.org/10.1186/1748-5908-5-69

McIlroy, P. A., King, R. S., Garrouste-Orgeas, M., Tabah, A., & Ramanan, M. (2019). The Effect of ICU Diaries on Psychological Outcomes and Quality of Life of Survivors of Critical Illness and Their Relatives: A Systematic Review and Meta-Analysis. *Critical Care Medicine*, *47*(2), 273–279. https://doi.org/10.1097/CCM.0000000000003547

Mitchell, M. L., Shum, D., Mihala, G., Murfield, J. E., & Aitken, L. M. (2018). Long-term cognitive impairment and delirium in intensive care: A prospective cohort study. *Australian critical care : official journal of the Confederation of Australian Critical Care Nurses*, *31*(4), 204–211. https://doi.org/10.1016/j.aucc.2017.07.002

Munn, Z., Peters, M., Stern, C., Tufanaru, C., McArthur, A., & Aromataris, E. (2018). Systematic review or scoping review? Guidance for authors when choosing between a systematic or

scoping review approach. *BMC Medical Research Methodology*, *18*(1), 143. https://doi.org/10.1186/s12874-018-0611-x

Needham, D. M., Wozniak, A. W., Hough, C. L., Morris, P. E., Dinglas, V. D., Jackson, J. C., Mendez-Tellez, P. A., Shanholtz, C., Ely, E. W., Colantuoni, E., Hopkins, R. O., & National Institutes of Health NHLBI ARDS Network (2014). Risk factors for physical impairment after acute lung injury in a national, multicenter study. *American Journal of Respiratory and Critical Care Medicine*, *189*(10), 1214–1224. https://doi.org/10.1164/rccm.201401-0158OC

Nielsen, A. H., Angel, S., Egerod, I., Lund, T. H., Renberg, M., & Hansen, T. B. (2020). The effect of family-authored diaries on posttraumatic stress disorder in intensive care unit patients and their relatives: A randomised controlled trial (DRIP-study). *Australian Critical Care: official Journal of the Confederation of Australian Critical Care Nurses*, *33*(2), 123–129. https://doi.org/10.1016/j.aucc.2019.01.004

Ohtake, P. J., Lee, A. C., Scott, J. C., Hinman, R. S., Ali, N. A., Hinkson, C. R., Needham, D. M., Shutter, L., Smith-Gabai, H., Spires, M. C., Thiele, A., Wiencek, C., & Smith, J. M. (2018). Physical Impairments Associated With Post-Intensive Care Syndrome: Systematic Review Based on the World Health Organization's International Classification of Functioning, Disability and Health Framework. *Physical therapy*, *98*(8), 631–645. https://doi.org/10.1093/ptj/pzy059

Paintain, E., & Cassidy, S. (2018). First-line therapy for post-traumatic stress disorder: A systematic review of cognitive behavioural therapy and psychodynamic approaches. *Counselling and psychotherapy research*, *18*(3), 237–250. https://doi.org/10.1002/capr.12174

Pandharipande, P. P., Girard, T. D., Jackson, J. C., Morandi, A., Thompson, J. L., Pun, B. T., Brummel, N. E., Hughes, C. G., Vasilevskis, E. E., Shintani, A. K., Moons, K. G., Geevarghese, S. K., Canonico, A., Hopkins, R. O., Bernard, G. R., Dittus, R. S., Ely, E. W., & BRAIN-ICU Study Investigators (2013). Long-term cognitive impairment after critical illness. *The New England Journal of Medicine*, *369*(14), 1306–1316. https://doi.org/10.1056/NEJMoa1301372

Parker, A. M., Sricharoenchai, T., Raparla, S., Schneck, K. W., Bienvenu, O. J., & Needham, D. M. (2015). Posttraumatic stress disorder in critical illness survivors: a metaanalysis. *Critical Care Medicine*, *43*(5), 1121–1129. https://doi.org/10.1097/CCM.0000000000000882

Rawal, G., Yadav, S., & Kumar, R. (2017). Post-intensive Care Syndrome: an Overview. *Journal of Translational Internal Medicine*, *5*(2), 90–92. https://doi.org/10.1515/jtim-2016-0016

Rengel, K. F., Hayhurst, C. J., Pandharipande, P. P., & Hughes, C. G. (2019). Long-term Cognitive and Functional Impairments After Critical Illness. *Anesthesia and analgesia*, *128*(4), 772–780. https://doi.org/10.1213/ANE.0000000000004066

Righy, C., Rosa, R. G., da Silva, R., Kochhann, R., Migliavaca, C. B., Robinson, C. C., Teche, S. P., Teixeira, C., Bozza, F. A., & Falavigna, M. (2019). Prevalence of post-traumatic stress disorder symptoms in adult critical care survivors: a systematic review and meta-analysis. *Critical care (London, England)*, *23*(1), 213. https://doi.org/10.1186/s13054-019-2489-3

Rousseau, A. F., Prescott, H. C., Brett, S. J., Weiss, B., Azoulay, E., Creteur, J., Latronico, N., Hough, C. L., Weber-Carstens, S., Vincent, J. L., & Preiser, J. C. (2021). Long-term

outcomes after critical illness: recent insights. *Critical care (London, England)*, *25*(1), 108. https://doi.org/10.1186/s13054-021-03535-3

Ruhl, A. P., Lord, R. K., Panek, J. A., Colantuoni, E., Sepulveda, K. A., Chong, A., Dinglas, V. D., Shanholtz, C. B., Pronovost, P. J., Steinwachs, D. M., & Needham, D. M. (2015). Health care resource use and costs of two-year survivors of acute lung injury. An observational cohort study. *Annals of the American Thoracic Society*, *12*(3), 392–401. https://doi.org/10.1513/AnnalsATS.201409-422OC

Spinazzola, J., Blaustein, M., & van der Kolk, B. A. (2005). Posttraumatic stress disorder treatment outcome research: The study of unrepresentative samples? Journal of Traumatic Stress,18,425–436. doi:10.1002/jts.20050

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., Lewin, S., … Straus, S. E. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of internal medicine*, *169*(7), 467–473. https://doi.org/10.7326/M18-0850

Umberger R. (2019). What is the best core measure after critical illness when the IES-R is no longer accessible for new researchers?. *Critical care (London, England)*, *23*(1), 313. https://doi.org/10.1186/s13054-019-2595-2

van den Born-van Zanten, S. A., Dongelmans, D. A., Dettling-Ihnenfeldt, D., Vink, R., & van der Schaaf, M. (2016). Caregiver strain and posttraumatic stress symptoms of informal caregivers of intensive care unit survivors. *Rehabilitation Psychology*, *61*(2), 173–178. https://doi.org/10.1037/rep0000081

Wade, D. F., Moon, Z., Windgassen, S. S., Harrison, A. M., Morris, L., & Weinman, J. A. (2016). Non-pharmacological interventions to reduce ICU-related psychological distress: a systematic review. *Minerva Anestesiologica*, *82*(4), 465–478.

Wade, D. M., Mouncey, P. R., Richards-Belle, A., Wulff, J., Harrison, D. A., Sadique, M. Z., Grieve, R. D., Emerson, L. M., Mason, A. J., Aaronovitch, D., Als, N., Brewin, C. R., Harvey, S. E., Howell, D., Hudson, N., Mythen, M. G., Smyth, D., Weinman, J., Welch, J., Whitman, C., … POPPI Trial Investigators (2019). Effect of a Nurse-Led Preventive Psychological Intervention on Symptoms of Posttraumatic Stress Disorder Among Critically Ill Patients: A Randomized Clinical Trial. *JAMA*, *321*(7), 665–675. https://doi.org/10.1001/jama.2019.0073

White, D. B., Angus, D. C., Shields, A. M., Buddadhumaruk, P., Pidro, C., Paner, C., Chaitin, E., Chang, C. H., Pike, F., Weissfeld, L., Kahn, J. M., Darby, J. M., Kowinsky, A., Martin, S., Arnold, R. M., & PARTNER Investigators (2018). A Randomized Trial of a Family-Support Intervention in Intensive Care Units. *The New England Journal of Medicine*, *378*(25), 2365–2375. https://doi.org/10.1056/NEJMoa1802637

Wild, J., & Gur, R. C. (2008). Verbal memory and treatment response in post-traumatic stress disorder. *The British journal of psychiatry : the journal of mental science*, *193*(3), 254–255. https://doi.org/10.1192/bjp.bp.107.045922

Williams, T., Phillips, N. J., Stein, D. J., & Ipser, J. C. (2022). Pharmacotherapy for post traumatic stress disorder (PTSD). *The Cochrane database of systematic reviews*, *3*(3), CD002795. https://doi.org/10.1002/14651858.CD002795.pub3

Wintermann, G.-B., Brunkhorst, F. M., Petrowski, K., Strauss, B., Oehmichen, F., Pohl, M., & Rosendahl, J. (2015). Stress disorders following prolonged critical illness in survivors of

severe sepsis. *Critical Care Medicine*, *43*(6), 1213–1222. https://doi.org/10.1097/CCM.0000000000000936

Manuscript I

A neurobiological framework for the therapeutic potential of music and sound interventions for post-traumatic stress symptoms in critical illness survivors

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A neurobiological framework for the therapeutic potential of music and sound interventions for post-traumatic stress symptoms in critical illness survivors

Abstract

Overview: Post traumatic stress disorder (PTSD) has emerged as a severely debilitating psychiatric disorder associated with critical illness. Little progress has been made in the treatment of post-intensive care unit (ICU) PTSD. **Aim**: To synthesize neurobiological evidence on the pathophysiology of PTSD and the brain areas involved, and to highlight the potential of music to treat post-ICU PTSD. **Methods**: Critical narrative review to elucidate an evidence-based neurobiological framework to inform the study of music interventions for PTSD post-ICU. Literature searches were performed in PubMed and CINAHL. The Scale for the Assessment of Narrative Review Articles (SANRA) guided reporting. **Results**: A dysfunctional HPA axis feedback loop, an increased amygdalic response, hippocampal atrophy, and a hypoactive prefrontal cortex contribute to PTSD symptoms. Playing or listening to music can stimulate neurogenesis and neuroplasticity, enhance brain recovery, and normalize stress response. Additionally, evidence supports effectiveness of music to improve coping and emotional regulation, decrease dissociation symptoms, reduce depression and anxiety levels, and overall reduce severity of PTSD symptoms. **Conclusion**: Despite the lack of music interventions for ICU survivors, music has the potential to help people suffering from PTSD by decreasing amygdala activity, improving hippocampal and prefrontal brain function, and balancing the HPA-axis.

Keywords: Music, Post traumatic stress disorder, critical illness, neurobiology, autonomic nervous system, limbic system.

Introduction

Ongoing advancements in Intensive Care Unit (ICU) technology and evidence-based practice have significantly reduced ICU mortality. However, the intense stress and adverse emotions experienced during hospitalization in an ICU have long term effects on survivors' physiological and psychological well-being (Annachiara et al., 2018; Desai et al., 2011; Needham et al., 2012). Post Traumatic Stress Disorder (PTSD) has emerged as a major long-term complication of critical illness, along with depression and anxiety disorders (Desai et al., 2011; Needham et al., 2012; Parker et al., 2015; Wintermann et al., 2015). Conservative estimates predict that one in every five survivors of critical care exhibit clinically significant symptoms of PTSD in the first year following ICU discharge (Righy et al., 2019). Some variance in prevalence estimates exists, from 5 to 63% depending upon the time of assessment, screening tool and population (Davydow, Gifford et al., 2008; Griffiths et al., 2007; Jackson et al., 2007; Parker et al., 2015; Rabiee et al., 2016; Wade et al., 2013). The psychological impairments following critical illness constitute a significant public health issue (Rousseau et al., 2021). Although integrative interventions and music therapy during the acute ICU stay have received some attention (Umbrello et al., 2019; Wade et al., 2013), there is a paucity of studies exploring the effects of music post-ICU discharge. This review seeks to raise awareness regarding this overlooked area, gather and report all current literature on this topic, and to propose an evidence-based theoretical framework to guide music and sound interventions for ICU survivors.

PTSD is characterized by symptoms including: intrusive memories, hyper-arousal, avoidance of trauma-related stimuli, and negative alterations in mood or cognition that develop following exposure to traumatic life events. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (2013) criteria for diagnosis, PTSD can be diagnosed if an individual

is exposed to actual or threatened serious injury or death. Events such as critical illness, ICU admission and related ICU treatments such as awareness during intubation can meet the first criteria for PTSD (American Psychiatric Association, 2013). The additional criteria include intrusive symptoms such as; a) persistently re-experiencing the event through nightmares or flashbacks, b) avoidance of trauma-related stimuli (they avoid remembering or thinking about the event and resist talking about how they feel about it), c) new negative alterations in mood or cognition (depressed mood, trouble concentrating and irritability) and d) hyperarousal (increase in arousal or anxiety that was not present prior to the trauma) that lasts more than 1 month and causes significant distress or changes in functionality (American Psychiatric Association, 2013). PTSD affects cognitive abilities such as memory and learning, and often leads to social withdrawal. PTSD influences quality of life in ICU survivors, affecting their lives in intensely negative ways, including their ability to work, study and even carry out daily activities of living (Desai et al., 2011; Jackson et al., 2014).

The combination of life-threatening illness or injury, along with the impact of potentially traumatic experiences in the ICU can contribute to the development of PTSD (Davydow, Desai et al., 2008; Davydow, Gifford et al., 2008; Girard et al., 2007). Potential traumatic experiences during critical illness are associated with awareness during painful procedures such as intubation, sense of helplessness, hallucinations, loss of control and fear of death (Gezginci et al., 2020; Gültekin et al., 2018; McGiffin et al., 2016; Zengin et al., 2020). The specific ICU-related risk factors include in-hospital stress, ICU length of stay and mechanical ventilation, delirium, use of sedatives and analgesics, high disease severity and negative ICU experience (Amra et al., 2018; Lee et al., 2020; Parker et al., 2015). Pre-existing psychopathology is the only pre-ICU factor associated with PTSD in the ICU survivors.

Aim

This review aimed to summarize neurobiological evidence on the pathophysiology of PTSD and the areas of the brain involved, as well as some of the effects of music on PTSD and ICU survivors to highlight potential mechanisms and effects of music on individuals suffering from post-ICU PTSD. Delineating an evidence-based theoretical framework of the effects of music for rehabilitation after critical illness can inform interventions that improve survivors' psychological well-being and health outcomes.

Methods

We used a critical narrative review methodology as this was deemed most appropriate for the delineation of a theoretical framework on music effects on PTSD post-ICU**.** As there is a lack of guidelines for narrative reviews, we followed methodological recommendations by Ferrari (Ferrari et.al., 2015). We searched current research evidence on the pathophysiology of PTSD, especially pertaining to alterations in specific brain regions, and juxtaposed these findings with the neurobiological effects of music therapy in the brain, and its effects on neuropsychiatric conditions. We used a combination of search terms for music and PTSD to conduct keyword searches in PubMed and CINAHL databases spanning the time period from January 2000 to October 2021. The databases were searched individually for the following keyword combinations: (music or sound or audio or melody or playing or improvisation or song writing or singing or song or GIM or Guided Imagery and Music) AND (PTSD or post-traumatic stress disorder or stress disorder).

Inclusion criteria included: systematic syntheses of evidence, primary research studies in humans regardless of methodology, studies that addressed the pathophysiology and neurobiology of PTSD, and studies that addressed the physiological effects of music on brain function. Studies

that were not based on research evidence, that included non-human participants, and were not reported in English were excluded. Due to the scarcity of literature on the topic, we did not include any chronological criteria. We did not employ a formal approach to quality appraisal. We extracted and synthesized results of PTSD-related alterations on specific brain structures, and the impacts and mechanisms of music effects on these brain structures, as well as evidence on the effects of music on related neuropsychiatric entities. The Scale for the Assessment of Narrative Review Articles (SANRA) guided reporting (Baethge et.al., 2019).

Results

Our search strategy yielded 363 articles addressing the neurobiology of PTSD, 841 articles addressing the effects of music on PTSD and 61 articles on the neurobiological effects of music therapy in the brain.

Pathophysiology of PTSD

To summarize evidence on how the brain is affected by PTSD, it is essential to examine the key structures of the brain that are associated with how memories are stored, and how stimuli are associated with emotion. These key structures include: the prefrontal cortex (PFC), the amygdalae, and the hippocampus. Alterations in these areas of the brain are observed across various studies assessing PTSD (Boccia et al., 2016; Flor et al., 2014). Since the Hypothalamus-pituitary-adrenal axis **(**HPA axis) is the primary endocrine mediator of stress responses, studies have also illustrated the role of the HPA in the onset and perpetuation of PTSD (Dunlop et al., 2019; Herman et al., 2016; Myers et al., 2014).

Table 1. Summary of studies employing neuroimaging measurements

Authors, date	**Imaging techniques**	**Brain measurements**
Boccia, et al., 2016	Functional magnetic resonance imaging OR positron emission tomography	Structural brain changes related to PTSD symptomatology Functional connectivity of a brain region

Etkin & Wager, 2007	Functional magnetic resonance imaging OR positron emission tomography	Functional activity of a brain region
Coburn, et al., 2018	Structural magnetic resonance imaging	Structural brain changes
McNerney, et al., 2018	Neuroimaging	Structural brain scan
Postel, et al., 2021	High-resolution magnetic resonance imaging	Structural changes in hippocampal subfields
Gilbertson, et al., 2002	Structural magnetic resonance imaging	Image acquisition and volumetric analyses of hippocampus
Smith, et al., 2005	Magnetic resonance images	Hippocampal volume
van Rooij, et al., 2015	Magnetic resonance imaging	Hippocampal volume
Wang, et al., 2010	High-resolution magnetic resonance imaging	Volumes of hippocampal subfields
Grupe, et al., 2019	Structural magnetic resonance imaging	Volume of the hippocampus and amygdala
Selemon, et al., 2019	Functional magnetic resonance imaging	Structural and functional changes in brain
Stevens, et al., 2013	Functional magnetic resonance imaging	Functional activity of amygdala and prefrontal cortex Amygdala- prefrontal cortex connectivity
Liu, et al., 2021	3-Tesla magnetic resonance imaging	Functional connectivity of the amygdala and its subregions.
Delgado, et al., 2008	Functional magnetic resonance imaging	Functional connectivity and emotional regulation
Johnstone, et al., 2007	Functional magnetic resonance imaging	Functional activity of amygdala and prefrontal cortex
Urry, et al., 2006	Functional magnetic resonance imaging	Brain activity in ventral lateral, dorsolateral, and dorsomedial regions of PFC and amygdala
Xiong, et al., 2013	Event-related functional magnetic resonance imaging	Activity in the inferior frontal cortex, inferior parietal lobule, insula and putamen, posterior cingulate cortex, and amygdala in responses to negative stimuli
Matsuo, et al., 2003	Near-infrared spectroscopy	Hemodynamic response of the prefrontal cortex during a cognitive task

Mary et al., 2020	Functional magnetic resonance imaging	Mechanisms of memory suppression after trauma

The Hypothalamus-pituitary-adrenal axis

The HPA axis involves a complex set of interactions among the hypothalamus, the pituitary gland, and the adrenal gland that determines the level of circulating cortisol. Stress triggers an HPA and sympathetic nervous system (SNS) response. Upon perception of a stressful stimulus, norepinephrine and indirect limbic inputs from the hippocampus, prefrontal cortex, and amygdala stimulate neurons in the paraventricular nucleus (PVN) of the hypothalamus that contain corticotropin releasing factor (CRF), leading to activation of the HPA axis and release of adrenocorticotropic hormone (ACTH) into the systemic circulation. ACTH then binds to melanocortin 2 receptors in the zona fasciculata of the adrenal cortex and stimulates release of glucocorticoids (specifically cortisol). Activation of the HPA axis is modulated by pituitary adenylate cyclase-activating polypeptide (PACAP), which appears to mediate the production of CRF. PACAP is also involved in modulation of the sympathetic nervous system (SNS) response (Chu et.al., 2021).

The SNS contributes to the flight or fight response by signaling the adrenal medulla to release catecholamines (epinephrine and norepinephrine) and enkephalins. Cortisol, catecholamines and enkephalins together stimulate a series of effects such as enhancing glucose availability, regulating immune system and brain function, and impacting electrolyte balance to manage stressors (Myers et al., 2014). Simultaneously, several brain structures control the HPA axis activity. Specifically, both the hippocampus and PFC impede the CRF neurons in the PVN of the hypothalamus. In contrast, the amygdala triggers CRF neurons in the PVN. Cortisol regulates HPA-axis activity by generating negative feedback to both the hypothalamus and the anterior pituitary.

Cortisol acts as the primary molecule to enable the stress response, as well as prevent ongoing HPA axis activity. The function of the HPA axis is controlled by two factors: a) the effectiveness and b) number of glucocorticoid receptors in the pituitary and hypothalamus (Dunlop et al., 2019; Ehlert et al., 2001), which regulate both CRF and ACTH release. However, if the negative feedback cycle of the HPA axis is disrupted, either due to the overactivity of CRF or due to hypersensitivity to glucocorticoids, the production of cortisol continues. This negative feedback system appears to be compromised in patients with PTSD. A metanalysis of 24 studies examining six HPA-axis genes in PTSD patients demonstrated involvement of two genes: a) NR3C1 associated with the encoding of glucocorticoid receptor, and b) FKBP5 linked with regulating the affinity of the glucocorticoid receptor (Sheerin et al., 2020). Moreover, persistent exposure to stressful events leads to multiple such cycles in a single day, preventing the HPA axis to returning baseline (Nickel et al., 2021). The aberrant stress response resulting from an overactive and prolonged HPA axis response increases stress-like symptoms in people with PTSD (Sherin et al., 2011). Moreover, the over-production of cortisol generates a state of toxic stress that changes the physical structure and function of the amygdala, hippocampus, and PFC (Fig. 1).

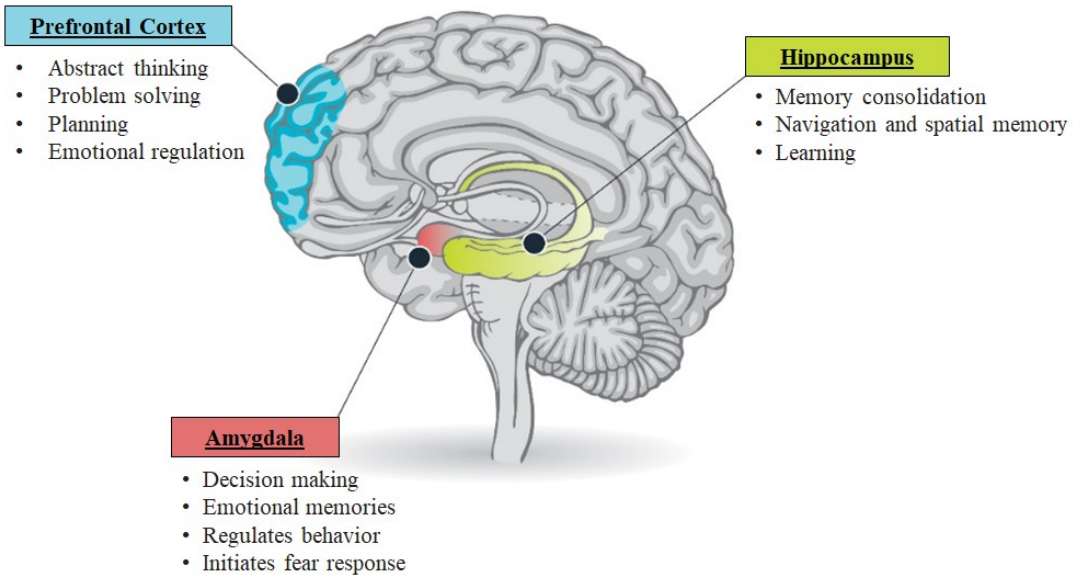

Figure 1. Brain structures involved in emotional regulation and fear response. Adapted from: Stress and the brain. https://turnaroundusa.org/wp-content/uploads/2020/03/Stress-and-the-Brain_Turnaround-for-Children-032420.pdf

The amygdalae

The amygdalae are a subcortical collection of nuclei situated in the anterior temporal lobe of each hemisphere, projecting to brainstem and hypothalamic regions. The amygdalae play a critical role in emotional processing and generation of fear responses. In particular, amygdalae are associated with the execution of the physical, autonomic, and musculoskeletal components of the emotional response. Moreover, they have connections with other emotional centers in the brain. The amygdalae process the stressful events resulting in the release of cortisol through HPA- axis activation. In case of an aberrant HPA axis feedback cycle, the continuous cortisol release enhances the amygdala's ability to communicate within and with other brain structures (Fuchs et al., 2014; Sherin et al., 2011). This makes the amygdalae more receptive to perceived threat. A metanalysis of fifteen functional imaging studies investigating PTSD patients demonstrated significant hyperactivation of the amygdalae (Etkin et al., 2007).

The hyperactive amygdalae shift the brain's processing mode from the thoughtful prefrontal cortex pathway to its own rapid, emotional, and reactive pathway (Arnsten et al., 2009; Chetty et al., 2014). Thus, the hyperactive amygdala promotes hypervigilance and impair discrimination of threatening stimuli (Sherin et al., 2011). This is a mechanism involved in the increased hyperawareness to stimuli that are not even related to the trauma experience in individuals with PTSD.

The Hippocampus

The hippocampus is an extension of the cerebral cortex situated deep within the temporal lobe. The hippocampus plays a crucial role in the consolidation of information from short-term

memory to long-term memory. It is also involved in the neuroendocrine regulation of stress hormones. Alterations in the structure and function of the hippocampus are observed in several neurological and psychiatric disorders (Coburn et al., 2018; Sherin et al., 2011). Boccia et al. (2016) through functional magnetic resonance imaging observed hypoactive hippocampus among participants with PTSD. The hippocampus has projections to the hypothalamus and is involved in the regulation of adrenocorticotropic hormones. Therefore, hypo-activity of the hippocampus may result in increased HPA axis activity (McNerney et al., 2018).

Traumatic stressors have also been shown to alter hippocampal dendritic morphology and inhibit neurogenesis in the hippocampus (Anand et al., 2012; Coburn et al., 2018; Kim et al., 2015; Kim & Yoon,1998). Chronic stress rapidly reduces the number of dendritic spines and branches of pyramidal neurons in the Cornu Ammonis subfields 3 (CA3) and compromises the integrity of CA1, which is involved in the persistence and re-experiencing of traumatic memories (Postel et al., 2021; Warner-Schmidt & Duman, 2006). For example, early magnetic resonance imaging studies demonstrated smaller hippocampal volumes in Vietnam Veterans with PTSD compared with controls (Gilbertson et al., 2002; Gilbertson et al., 2007; Smith et al., 2005; van Rooij et al., 2015; Wang et al., 2010). Small hippocampal volumes were associated with the severity of trauma and memory impairments in these studies. Stress also suppresses the production of new granule neurons in the dentate gyrus regions of the hippocampus (Schoenfeld et al., 2012). Evidence also shows that small hippocampal volumes are involved in increased susceptibility to stress and trauma (Grupe et al., 2019). Moreover, prolonged HPA axis activation generates various neurobiological changes in the hippocampus that influence the hippocampal functions, such as learning and memory functioning (Kim et al., 2015).

Altogether, these changes can result in generalizing the fear from the traumatic event to learned-fear in situations that are not related to the traumatic event, with hypervigilance and avoidance behaviors. Thus, the person with PTSD has a difficult time distinguishing between safe and unsafe stimuli and re-experiences a physiological and emotional toll similar to the traumatic event. This results in hypervigilance (Fuchs et al., 2014), exaggerated stress response and inability to prevent other fear associations (Chetty et al., 2014). Moreover, the effects on the hippocampus also inhibit learning and recall of previously stored memories (McAuley et al., 2009), contributing to repressed memories in PTSD patients.

The pre-frontal cortex

PFC is vitally involved in executive functions such as concentration, organization, judgement, reasoning, problem solving, decision-making, creativity, emotional regulation, and abstract thinking. Chronic exposure to stress impairs prefrontal cortex functioning, which leads to aberrant stress responses and maladaptive coping. Decreased volumes of the frontal cortex are associated with significant hypoactivation of the PFC in individuals with PTSD (Etkin et al., 2007; Selemon et al., 2019). There are dense white matter connections between the ventral region of PFC and the amygdalae that facilitate bi-directional communication between these two areas. Amygdalic activity is inhibited through the PFC (Delgado et al., 2008; Johnstone et al., 2007; Liu et al., 2021; Stevens et al., 2013; Urry et al., 2006). Therefore, a hypoactive PFC in individuals with PTSD may impair regulation of emotional processing in the amygdalae (Xiong et al., 2013). Besides this, prefrontal dysfunction also results in reduced ability to concentrate and regulate executive functions (Matsuo et al., 2003; Sherin et al., 2011). Thus, the hypoactivity of the prefrontal cortex can explain some of the symptoms of PTSD such as the inability to focus, solve

problems and guide thoughts or emotions using working memory (Arnsten et al., 2009; Mary et al., 2020).

Table 2. Summary of PTSD relevant brain areas, structural changes, and effects on behavior.

Brain Areas	**Neurobiological Changes**	**Effects on behavior**
Hippocampus	Reduced volume and activity, Reduced dendritic spines and branches of pyramidal neurons in CA3, and Inhibited neurogenesis	Exaggerated activation and inability to terminate stress response, impaired extinction of fear conditioning, non-discrimination between safe/unsafe stimuli, and repressed memories
Amygdala	Increased reactivity, and Altered communication with other brain regions	Promotes hypervigilance and impairs discrimination of threat
Prefrontal Cortex (PFC)	Reduced volume and activity, and Disrupted communication with amygdalae	Decreased reactivity of PFC to exert inhibitory control over stress responses and dysfunctional thought process and decision making

Music Therapy

Music therapy is a systematic process of intervention wherein the therapist helps the client to promote health, using musical experiences, and the relationships that develop through them as dynamic forces of change (Bruscia, 1998). Music not only can evoke feelings, but also engages and motivates people to connect to others and offers a medium of nonverbal communication (Canadian Association of Music Therapists, 2020). Music therapy is a type of expressive arts therapy that uses music to improve and maintain the physical, psychological, and social well-being of individuals and involves a broad range of activities, such as listening to music, singing, and playing a musical instrument (Canadian Association of Music Therapists, 2020).

Active music therapy engages patients in some form of music-making, such as vocalizing, singing, playing instruments, song writing or composing, and conducting (Canadian Association of Music Therapists, 2020). Receptive music therapy guides patients or clients in listening or

responding to live or recorded music through dancing or other movement to music, or lyric discussion (Canadian Association of Music Therapists, 2020; Grocke et al., 2007).

Effect of Music in neuropsychiatric conditions and PTSD

Various music and sound interventions have been used to improve health outcomes in a broad spectrum of psychological and neurological disorders (Blanaru et al., 2012; Golden et al., 2021; Wang & Agius, 2018; Xu et al., 2017). Music therapy has demonstrated significant effectiveness for reduction of depression in people with dementia (van der Steen et al., 2017; Wang & Agius, 2018) and improvement of mobility in people with stroke (Magee et al., 2017). A systematic review of music therapy delivered by a professional music therapist revealed the efficiency of music to improve social interaction and communication skills in children with autism spectrum disorder (Geretsegger et al., 2014). Moreover, there is evidence that music therapy in addition to standard care improved mental state and social functioning in schizophrenia patients (Geretsegger et al., 2017; Wang & Agius, 2018).

A meta-ethnography of 46 qualitative studies found that participatory music engagement, music actively made by the participant, including singing, and not limited by musical genre such as classical, or jazz improved well-being by facilitating self-development, providing respite from problems, and fostering social connections (Perkins et al., 2020). There is growing evidence that music therapy can abate the stress response, decrease anxiety, and induce an overall relaxation response by reducing stress-inducing stimuli. A recent meta-analytic study by Witte et al. (2020) revealed effectiveness of music interventions to relieve stress in a variety of settings, including mental health, polyclinic medical settings, medical surgery, and everyday life. The study's findings demonstrated that pre-recorded relaxation music without lyrics could reduce physiological stress symptoms such as heart rate, blood pressure, and stress-related hormones, as well as psychological

stress symptoms such as anxiety, nervousness, restlessness, and feelings of worry (de Witte et al., 2020). McKinney & Honig (2017), in a systematic review across populations, examined effects from randomized and non-randomized controlled trials and found a medium to large effect of guided imagery and western classical music on various psychological measures including anxiety, and mood disturbance. A Cochrane review by Bradt et al., (2013) demonstrated beneficial effect of patient-selected music from different styles of music such as jazz, easy listening, country and western, or classical music on preoperative anxiety and recommended its use as an alternative to sedative drugs. Another review of the literature by Hole et al., (2015) confirmed that Chinese classical music reduced postoperative pain, anxiety, and analgesia use and increased patient satisfaction.

The effect of music and sound interventions has also been explored in ICU patients [13]. Various forms of music interventions in ICU populations are found beneficial in reducing ICU-related anxiety and in-hospital stress (Umbrello et al., 2019; Wade et al., 2016). In mechanically ventilated patients, patient-directed music therapy is associated with lower anxiety scores, sedation frequency, and sedation intensity when compared to usual care (Chariyawong et al., 2016; DellaVolpe et al., 2015; Gullick et al., 2015; Mofredj, et al., 2016). A majority of included studies used music that contains simple repetitive rhythms, low pitch, slow tempos, harmony and lack percussive instruments and vocals. A literature review by Hetland et al. (2015) indicated that relaxing music such as nature-based sounds, classical, and easy listening can help manage pain, agitation, delirium, posttraumatic stress disorder (PTSD), anxiety, and depression in ICU patients by reducing the need for sedatives during mechanical ventilation, length of stay, and physiologic signs of anxiety and biomarkers of the stress response. Moreover, implementing music interventions in usual care is free of adverse side effects and can also reduce ICU costs. A recent

study by Chlan et al (2018) demonstrated that patient-directed music interventions can save about $2,000/patient and concurrently better manage anxiety with less sedative medication than usual care. However, to date the effect of music and sound interventions have not been explored in relation to the psychiatric disorders and PTSD after discharge from the ICU.

Despite this gap in evidence, music appears to be a promising adjunct in the treatment of PTSD (Blanaru et al., 2012). Evidence from various studies shows significant effect of individual and group music therapy in reduction of core PTSD symptoms and increase in social function among PTSD patients (Table 3). A systematic review on creative art therapy also pointed out the potential of relaxation music therapy to creatively process, cope, and recover from PTSD (Baker et.al., 2018). A mixed method study by Story and Beck (2017) reported experiencing classical music as a tool for coping with PTSD symptoms, particularly to regulate emotions, decrease arousal, express repressed feelings, and connect with others. Moreover, group music therapy in adult psychiatric patients with persistent PTSD, who had been unable to benefit from cognitive behavioral therapy CBT, showed a significant decrease of all dimensions of PTSD symptoms (Carr et al., 2012). The study explored therapist guided music improvisation technique using a variety of musical instruments such as xylophones, maracas, Indian bells, gato drums, djembe, tone bars, guitar, piano and cabassas.

Empirical evidence suggests that music therapy may reduce prominent symptoms of posttraumatic stress, including emotionally dysregulating intrusions, avoidance, negative alterations in mood, and arousal. A study by Zergani & Naderi (2016) demonstrated beneficial effects of Iranian traditional music on quality of life and anxiety symptoms among hospitalized veterans with PTSD. A double blinded randomized control trial conducted by Pourmovahed et al., (2021) demonstrated that listening to nonverbal music can significantly reduce severity of PTSD

in mothers of premature infants hospitalized in NICU and promote emotional bonding between the mother and baby. The music included the sound of rain, sea, and nature with a slow, gentle, and soothing rhythm. Another randomized controlled trial that examined the effects of music therapy on symptoms of PTSD among prison inmates demonstrated significant decrease in PTSD-symptoms (Macfarlane et al., 2019). A mixed method study examining the efficacy of group drumming therapy in military veterans with PTSD indicated a significant reduction of specific symptoms such as isolation, lack of connectedness, avoidance of traumatic memories, rage, and anxiety (Bensimon et al., 2008). A mixed method study on the feasibility of group music therapy for women with PTSD and complex PTSD found significant changes in the PTSD, dissociation, anxiety, and depression scales, indicating symptom reduction (Rudstam et al., 2017). The qualitative analysis of participant experiences revealed that music assisted in establishing contact with feelings and bodily sensations, as well as providing an experience of expansion, relaxation, and new energy. Furthermore, six participants no longer had a PTSD diagnosis after treatment as shown by PCL-5 cut-off values, which was sustained even at follow-up.

Music guided relaxation has also shown positive impact in reducing depression, PTSD and increasing sleep quality in veterans (Blanaru et al., 2012). In a naturalistic study of 102 women with complex PTSD, guided imaginary and classic music significantly reduced symptoms of extreme stress, dissociation, interpersonal problems, and sense of coherence (Maack et al., 2012). Another study demonstrated similar results of guided imaginary and classic music in refugees with PTSD. After sixteen GIM sessions, adult refugees showed positive improvements in PTSD symptoms, sleep quality, well-being, and social functioning (Beck et al., 2017). A recent randomized control trial with 74 refugees with PTSD, employing western classical music, New Age music, and music from the participants' own national culture showed improvements in quality

of life and fewer symptoms of psychological dissociation after music therapy (Beck et al., 2021). In addition, unlike the standard treatment, the positive effects of music and imagery were manifested even at 6 month follow up.

Table 3. Summary of evidence on the main effects of music interventions in patients experiencing PTSD symptomatology.

Author (s), year	Study design	Type of effect	Measure of effect	Interpretation of Main findings
Baker et al., 2018	Systematic Review of 7 interventional studies	Decrease in severity of PTSD	Effect sizes ranged from low-medium effect (PTSD measures used: IES-R and PTSD-8)	Significant reduction in symptoms of PTSD when there was ongoing therapist involvement compared to when there was little therapist or no therapist involvement.
Story & Beck, 2017	Mixed methods	Improved coping Improved emotional regulation Decrease in severity of PTSD	Change in PTSD symptoms, ES=1.0	Participants reported experiencing music as a tool for coping with PTSD symptoms, regulate emotions, decrease arousal, express repressed feelings, and connect with others.
Pourmovahed et al., 2021	Randomized control trial	Improved emotional regulation Decrease in severity of PTSD	Severity of the PTSD decreased significantly after the intervention in the experimental group ($F_{1,57} = 1046$, $p = 0.003$) Difference between the two groups ($F_{1,07} = 1058$, $p < 0.03$), confirmed	Listening to non-verbal music reduced severity of PTSD and the mother's stress consequently promoting emotional

		Decreased anxiety levels	significant effect of the non-verbal music on decreasing the PTSD severity	bonding between the mother and baby.
Bensimon et al., 2008	Mixed method	Improved emotional regulation Decreased anxiety levels	Reducing the client's self-reported anxiety during confrontation with feared stimuli Effect measures not reported	Coping with difficulties such as feelings of loneliness, harsh traumatic memories, outbursts of anger, and loss of control.
Carr et al., 2012	Mixed method study	Decrease in severity of PTSD Decrease in depression	IES-R significant reduction from baseline of (−17.20; 95%CI: [−24.94, −9.45; p = .0012]) Reduction in BDI-II symptom severity (−0.71)	Music and guided imagery can improve symptoms of Complex PTSD and dissociation, alleviate interpersonal problems, and enhance factors that promote health.
Rudstam et al., 2017	Mixed method study	Decrease in severity of PTSD Decrease in depression Decreased anxiety levels Decreased dissociation symptoms	Pre-post Comparisons • PCL-5, ES=1.10 • DES-T, ES =0.85 • DES, ES=1.00 • HSC25-I, ES=1.17 • HSC25-II, ES=0.58 • PSOM, ES=0.24 Follow-up • PCL-5, ES=1.49 • DES, ES=0.92 • DES-T, ES =1.10	Significant decreases in PTSD symptoms with very large effect sizes, and dissociation with large effect sizes, and an increase in quality of life with small to medium effect size. Music helped establish contact with feelings and body sensations and provided an experience of

		Improved quality of life	• HSC25-I, ES=1.35 • HSC25-II, ES=0.74 • PSOM, ES=0.59	expansion, relaxation, and new energy.
Maack, 2012	Mixed method study	Decrease in severity of PTSD Decreased dissociation symptoms Improved quality of life	Kruskal-Wallis-Test shows that there was a significant difference in change of severity of symptoms between the groups ($p < .001$). KW test statistic not reported. Mann-Whitney Tests shows that there was a significant difference in change of severity of symptoms between the GIM and the control group ($U = 1.50$, $p < .001$).	The symptoms of the participants of the GIM group improved significantly more than the symptoms of the participants of the PITT group.
Beck et al., 2017	Pre-posttest study	Decrease in severity of PTSD Improved quality of life	Pre-post Comparisons • HTQ subscales, ES=1.17 • Avoidance, ES = 1.11 • Intrusion, ES =1.03 • Hypervigilance, ES =0.60 • WHO-5 Wellbeing scale, ES =0.18	Significant changes in positive directions on all four outcome measures, PTSD symptoms, sleep quality, well-being, and social functioning.

Macfarlane et al., 2019	Pre-posttest study	Decrease in severity of PTSD	Average reduction of PTSD symptoms of 38% between the entrance screening and the final point of the intervention, using PSS-I	A drop of ten points or more on PSS-I score for eight of the participants. Among which five had a final scored below PTSD threshold. Applicable in a complex clinical setting with a very mixed and treatment resistant population, who were not eligible for EMDR or another type of trauma treatment, at the moment of enrollment.
Blanaru et al., 2012	Mixed method study	Decrease in depression	Significant reduction in BDI score for depression following music relaxation compared with baseline [F (1,11) =14.8, P<0.003]	Music relaxation was found to be effective and led to significant improvements in sleep measures and significant reduction of depression score in PTSD patients.
Beck et al., 2021	Randomized control trial	Decreased dissociation symptoms Improved quality of life	Music group well-being, large effect size • ES = 0.58, p = .005 at end of treatment • ES =0.61, p = .004 at Follow up Psychoform dissociation, small to large effect size • ES= 0.35 at end of treatment	Small to large effect sizes in both psychological treatment group and music therapy group, with significant medium effect sizes, for well-being and psychoform

			• ES=0.71, p = .0002 at Follow up Psychological treatment group, well-being, small effect size • ES= 0.06 at end of treatment • small ES = 0.18 at follow up Psychoform dissociation, medium effect size • ES= 0.31 at end of treatment • ES=0.41 at Follow up	dissociation at follow-up. A high dropout rate of 40% occurred in the psychological treatment group, compared to 5% in the music therapy group.
Zergani & Naderi, 2016	Randomized control trial	Decreased anxiety levels Improved quality of life	Significant difference between experiment and control groups for anxiety symptoms (F - 13.67; p < 0.0001), STAI scale, and quality of life (F - 26.99; p < 0.0001), SF-36 scale	The effect of music remained stable even after one month of follow-up.

PCL-5: PTSD Checklist for DSM-5; DES: Dissociative Experience Scale; DES-T: Dissociative Experience Scale Taxon; HSCL-25: Hopkins Symptom Checklist; PSOMS: Positive State of Mind Scale; IES-R: Impact of Event Scale–Revised; PTSD-8: Post-traumatic Stress Disorder 8-item; BDI: Beck Depression Inventory, HTQ: Harvard Trauma Questionnaire; STAI: State-Trait Anxiety Inventory; SF-36: Short Form Health Survey is a 36-item; WHO-5: WHO Well-being Index; ES: Effect Size using Cohen's d

Mechanisms underlying the effects of music in PTSD

Musical stimuli stimulate neural networks associated with various functional domains, such as movement, cognition, communication, emotion, and social responses (Mclntosh & Thaut, 2010). Studies clearly demonstrate that instrumental music without lyrics, Chinese and Western music can evoke changes in emotion and stimulate the brain structures involved with motivation, reward, and emotion (Ding et al., 2019; Koelsch et al., 2014; Koelsch et al., 2020; Koelsch et al., 2013; Schaefer et al., 2017). There is evidence that music can provoke changes in individual emotions, hormone arousal, emotional motor expression, and action movements (Koelsch et al., 2014). The studies included in this analysis used various experimental approaches, such as investigating music-evoked experiences of intense pleasure, emotional responses to consonant or dissonant music, happy or sad music, joy- or fear-evoking music, musical expectancy violations and music-evoked tension. Listening to joyful dance-tunes has been shown to reduce stress and enhance emotional responses, such as joy and peace (Fukui & Toyoshima, 2008; Koelsch et al., 2013). In particular, music is observed to stimulate increase in blood–oxygen level dependent (BOLD) signals in the amygdala, and the hippocampus (Koelsch et al., 2013). A meta-analysis of functional neuroimaging studies (Koelsch et al., 2020) found that the amygdalae, hypothalamus, and hippocampus, which are vital parts of the brain in producing emotion and in experiencing PTSD symptoms, are stimulated by music. None of the included studies used music with lyrics. The ventral tegmental area (VTA), involved in dopamine production and release within the reward system, is also significantly activated by both unfamiliar musical pieces and participant's favorite music, in contrast, PFC activity was positively correlated with pleasure scores associated with music (Mavridis et al., 2015; Zatorre et al., 2015). However, favorite versus neutral music listening contrasts showed greater activation in healthy participants than depressed patients (Mavridis et al., 2015).

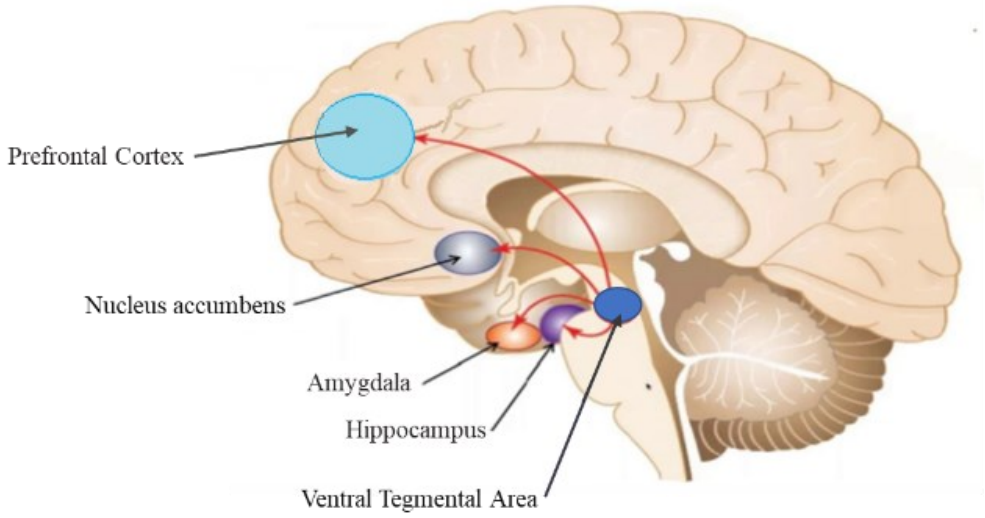

Figure 2. Music stimulates the mesocorticolimbic system. Specifically, it activates the nucleus accumbens, ventral tegmental area, hippocampus, amygdalae, and prefrontal cortex. Adapted from: Desai, R. (2019). Drug addiction. https://drrajivdesaimd.com/wp-content/uploads/2019/06/brain-and-drug-2.jpg

PTSD is characterized by hypervigilance associated with altered connectivity between the amygdalae and the hippocampus (Chetty et al., 2014). Communication between these brain areas is vital in the symptomatology of PTSD. There is evidence that participant's own favorite music to which they usually had a chill experience, can enhance the connection between the amygdalae, PFC, and the hippocampus (Koelsch et al., 2010). Moreover, contrast analysis of joy, fear and neutral musical stimuli revealed strongest BOLD signals in the superficial amygdala during joyful music such as classical music, Irish jigs, jazz, reggae, South American and Balkan music (Koelsch et al., 2013). Thus, music could potentially play a role in balancing the processing of stimuli and in reducing the amygdala's startle response so they can revert to the premorbid state. Moreover, attentive listening to musical clips played with piano or violin, can also stimulate PFC (Armony et al., 2015), and therefore can possibly recruit PFC to exert inhibitory control over amygdalic stress responses. Initiating communication between the amygdalae, PFC and hippocampus through

music can therefore not only mitigate the hypervigilance of PTSD but can also enhance cognitive processing of emotions.

Attentive listening to or playing music can stimulate neurogenesis and neuroplasticity in the brain (Fukui & Toyoshima, 2008; Mclntosh & Thaut, 2010; Reybrouck et al., 2018) which is relevant for individuals with PTSD who experience neuronal loss and impaired neurogenesis in parts of the limbic system. The increased hippocampal communication with the hypothalamus can also help balance the HPA axis (Reybrouck et al., 2018). There is evidence suggesting that musical training in healthy participants can stimulate the hippocampus, induce neurogenesis, and produce a larger hippocampus (Groussard et al., 2014; Guo et al., 2020; Olszewska et al., 2021). Altering the hippocampal volume can consequently increase positive emotions and regulate negative affect. Koelsch and Skouras (2014) reported increased functional connectivity between the hippocampus and hypothalamus, and amygdalae and nucleus accumbens during exposure to joyful music in healthy adults. The study used non-vocal joyful instrumental music from various epochs and styles. In addition, several studies on music-evoked emotions have reported activity changes in the hippocampus associated with a reduction of emotional stress associated with lowering of the cortisol level (Finn & Fancourt, 2018; Fukui & Toyoshima, 2008; Khan et al., 2018; Koelsch et al., 2011). Overall, 75% of these studies involved experimenter-selected music (classical, new age or easy listening, and world), while the other 25% involved self-selected music, either “entirely self-selected” or “quasi-self-selected”. Clinical studies, which included majority of ICU population, demonstrated a stress-reducing effect of music listening irrespective of genre, self-selection of the music, or duration of listening (Finn & Fancourt, 2018). Classical music demonstrated significant reduction in cortisol levels among mechanically ventilated ICU survivors (Khan et al., 2018).

Evidence suggests that active vs passive music therapy may have differential effects on patient engagement and receptivity. According to fMRI and PET scan studies, active music participation engages more parts of the brain than just listening to music (Yinger & Gooding, 2015). In a qualitative study, passive music therapy participants reported immediate therapeutic effect such as reduction in anxiety (Lynch et al., 2021). Active music therapy participants, on the other hand, described interactive session elements stimulating, alleviating anxiety through pleasant social interaction. Music improvisation (drum based) has been found to be effective in expressing and managing emotions among veterans with PTSD (Bensimon et al., 2008). Moreover, a systematic review showed that passive listening to relaxing music didn't seem to have any significant effects on PTSD symptoms, suggesting the importance of active music therapy to evoke change in PTSD patients (Baker et al., 2018). The researchers posited that specialist skills and ongoing therapeutic relationship is vital in reducing symptoms of PTSD.

However, music selection needs careful consideration. Music that the participant does not enjoy may result in a stress rather than a relaxation response. Moreover, music can trigger strong memories, which influence the affective response to music and can therefore modulate the therapeutic effects of music (Laura & Suvi Saarikallio, 2020). In the acute phase of critical illness, despite some controversy around the role of patients' music preferences, it appears that patient-directed music selection associates with better outcomes (Heiderscheit et al., 2014). In our review, several studies allowed participants to choose music from a variety of musical genres. However, participants' choices were restricted within the range of selections offered by the researchers. A systematic review on music interventions for mechanically ventilated patients reported participant dropout rates to be higher in researcher-selected music compared to patient-selected (Bradt & Dileo, 2014). Instead, studies involving a music therapist to assess patient music preferences have

reported no dropouts and a high degree of participant satisfaction (Beck et al., 2017; Beck et al., 2021; Blanaru et al., 2012). Therefore, self-selected music appears to be associated with both the effectiveness of music interventions and participant retention.

Basic psychoacoustic properties of music, such as pitch (high or low tone of sounds), rate (fast or slow speed of sounds), loudness (loud or soft intensity of sounds), mode (major or minor key), timbre, and rhythm have been shown to be important factors in the perception and induction of positive as well as negative emotional states. The music therapy research supports music containing slower tempo, low pitch, containing primarily string composition, regular rhythmic patterns, no extreme changes in dynamics, and no lyrics are associated with relaxation, joy, or peace (Parada-Cabaleiro et al., 2022). The tempo of 60-80 beats per minutes can help induce a state of relaxation and regulate emotions (Tan et al., 2012). A study by Beck et al., 2021 used predictable slow-tempo music to decrease arousal and induce relaxation in PTSD patients. In addition, the harmonic complexity of relaxing music should be consonant and remain within the diatonic key with a clear tonal center (Parada-Cabaleiro et al., 2022). Predictable music leads to positive responses such as reward, appraisal, and pleasantness thus may support the relaxation response. While dissonant and unexpected harmonies with frequent chord changes activate the amygdala and defeat the purpose of emotion regulation (Moore, 2013). Research has stated that music with less sharp timbres has been proven to induce relaxation (Parada-Cabaleiro et al., 2022). Possible instrumental arrangements include piano, cello, flute, marimba (Tan et.al., 2012). In addition, use of instrumental music over nature sounds can effectively induce relaxation.

As the HPA axis and the production of cortisol play a significant role in PTSD, music can be purposefully used to help regulate the stress response in PTSD. The effects of music on neurobiological aspects of PTSD are summarized in figures 3.

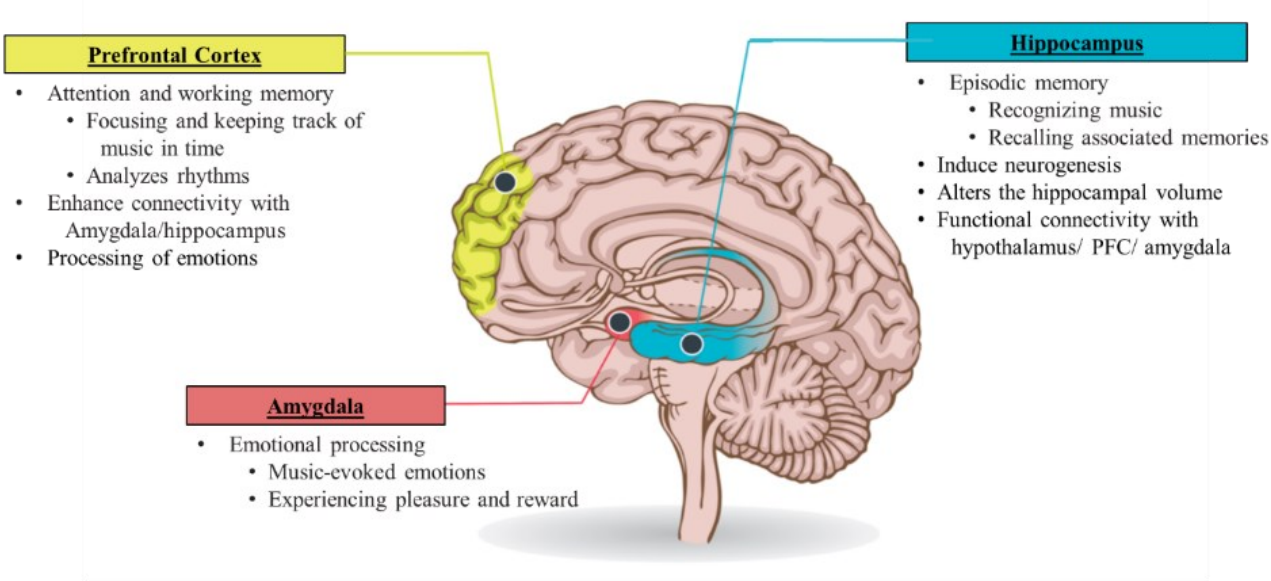

Figure 3. Main effects of music processing in amygdala, hippocampus, and prefrontal cortex. Adapted from: Cantor, P. (2021). The Stress of This Moment Might Be Hurting Kids' Development. https://turnaroundusa.org/pamela-cantor-m-d-pens-guest-post-for-education-next/

Conclusion

PTSD is part of the post-ICU syndrome and impairs the quality of life and functionality of increasing numbers of ICU survivors and their families worldwide. To date minimal progress has been made in the management of PTSD post-ICU. An impaired HPA axis feedback circle, an exaggerated amygdalic response, hippocampal atrophy and hypoactive prefrontal cortex accentuate PTSD symptoms preventing the healthy regulation of the fear response. Music can stimulate the hippocampus and amygdalae that are negatively impacted by stress. Music can also prompt neurogenesis and neuroplasticity within these brain structures and allow the brain to heal. In addition, music can stimulate communication between the amygdalae and PFC/hippocampus, which is vital in the regulation of stress responses. As a result, music can reduce the unnecessary stimulation of the amygdala, increase the effectiveness of both the hippocampus and prefrontal cortex, and balance the HPA-axis. Clinical evidence supports that relaxation music can help improve coping and psychological adaptation after discharge from ICU. In addition, both sound

and music interventions can decrease dissociation symptoms, reduce depression and anxiety levels, and overall reduce severity of PTSD symptoms. Thus, music could be a cost-effective, easy to access intervention to purposefully address PTSD after an ICU experience and improve the quality of life of both the ICU survivors and their families.

Future studies need to consider those neurobiological effects in planning and testing music interventions for PTSD in survivors of severe illness, such as critical illness. Moreover, elucidating the neurobiological effects of specific types of music, taking into account the intensity of music interventions (i.e., duration of sessions, repetition, length of intervention) and specific patient populations will be important in maximizing the impact of targeted music interventions for post-ICU survivors. Insights into the therapeutic potential of music by determining which types of music (considering individual experiences and preferences) are best suited to stimulate specific limbic brain structures can lead to a more systematic use of music in the therapy of PTSD.

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Reference

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Amra, S., John C., O., Mikhail, D., Dziadzko, V., Rashid, A., Tarun D., S., Rahul, K., Ann M., F., John D., F., Ronald, P., Ognjen, G., & Alejandro A., R. (2018) Potentially Modifiable Risk Factors for Long-Term Cognitive Impairment After Critical Illness: A Systematic Review. Mayo Clinic Proceedings, 93(1), 68–82. https://doi /10.1016/j.mayocp.2017.11.005

Anand, K. S., & Dhikav, V. (2012) Hippocampus in health and disease: An overview. Annals of Indian Academy of Neurology, 15(4), 239–246. https://doi.org/10.4103/0972-2327.104323

Annachiara, M., Pratik P., P., Timothy D., G., Mayur B., P., Christopher G., H., James C., J., Jennifer L., T., Rameela, C., Eugene Wesley, E., & Nathan E., B. (2018) Co-Occurrence of Post-Intensive Care Syndrome Problems Among 406 Survivors of Critical Illness*. Critical Care Medicine, 46(9), 1393–1401. https://doi /10.1097/CCM.0000000000003218

Armony, J. L., Aubé, W., Angulo-Perkins, A., Peretz, I., & Concha, L. (2015) The specificity of neural responses to music and their relation to voice processing: an fMRI-adaptation study. Neuroscience letters, 593, 35–39. https://doi.org/10.1016/j.neulet.2015.03.011

Arnsten A. F. (2009) Stress signalling pathways that impair prefrontal cortex structure and function. Nature Reviews. Neuroscience, 10(6), 410–422. https://doi.org/10.1038/nrn2648

Baethge, C., Goldbeck-Wood, S., & Mertens, S. (2019) SANRA-a scale for the quality assessment of narrative review articles. Research integrity and peer review, 4, 5. https://doi.org/10.1186/s41073-019-0064-8

Baker, F. A., Metcalf, O., Varker, T., & O'Donnell, M. (2018) A systematic review of the efficacy of creative arts therapies in the treatment of adults with PTSD. Psychological Trauma: Theory, Research, Practice and Policy, 10(6), 643–651. https://doi.org/10.1037/tra0000353

Beck, B. D., Messel, C., Meyer, S. L., Cordtz, T. O., Søgaard, U., Simonsen, E., & Moe, T. (2017) Feasibility of trauma-focused Guided Imagery and Music with adult refugees diagnosed with PTSD: A pilot study. Nordic Journal of Music Therapy, 1–20. https://doi.org/10.1080/08098131.2017.1286368

Beck, B. D., Meyer, S. L., Simonsen, E., Søgaard, U., Petersen, I., Arnfred, S., Tellier, T., & Moe, T. (2021) Music therapy was noninferior to verbal standard treatment of traumatized refugees in mental health care: Results from a randomized clinical trial. European Journal of Psychotraumatology, 12(1), 1930960. https://doi.org/10.1080/20008198.2021.1930960

Bensimon, M., Amir, D., & Wolf, Y. (2008) Drumming through trauma: Music therapy with post-traumatic soldiers. The Arts in Psychotherapy, 35(1), 34–48. https://doi.org/10.1016/j.aip.2007.09.002

Blanaru, M., Bloch, B., Vadas, L., Arnon, Z., Ziv, N., Kremer, I., & Haimov, I. (2012) The effects of music relaxation and muscle relaxation techniques on sleep quality and emotional measures among individuals with posttraumatic stress disorder. Mental Illness, 4(2), e13. https://doi.org/10.4081/mi.2012.e13

Boccia, M., D'Amico, S., Bianchini, F., Marano, A., Giannini, A. M., & Piccardi, L. (2016) Different neural modifications underpin PTSD after different traumatic events: an fMRI meta-analytic study. Brain imaging and behavior, 10(1), 226–237. https://doi.org/10.1007/s11682-015-9387-3

Bradt, J., & Dileo, C. (2014) Music interventions for mechanically ventilated patients. *The Cochrane database of systematic reviews*, *2014*(12), CD006902. https://doi.org/10.1002/14651858.CD006902

Bradt, J., Dileo, C., & Shim, M. (2013) Music interventions for preoperative anxiety. The Cochrane Database of Systematic Reviews, (6), CD006908. https://doi.org/10.1002/14651858.CD006908

Bruscia, K. E. Defining music therapy (2nd ed.). Barcelona Publishers (1998).

Canadian Association of Music Therapists (2020). About music therapy. Available online: https://www.musictherapy.ca/about-camt-music-therapy/about-music-therapy/ (accessed on 13 November 2021)

Cantor, P. (2021). The Stress of This Moment Might Be Hurting Kids' Development. Available online: https://turnaroundusa.org/pamela-cantor-m-d-pens-guest-post-for-education-next/ (accessed on 13 November 2021)

Carr, C., d'Ardenne, P., Sloboda, A., Scott, C., Wang, D., & Priebe, S. (2012 Group music therapy for patients with persistent post-traumatic stress disorder--an exploratory randomized controlled trial with mixed methods evaluation. Psychology and Psychotherapy), 85(2), 179–202. https://doi.org/10.1111/j.2044-8341.2011.02026.x

Chariyawong, P., Copeland, S., & Mulkey, Z. (2016). What is the role of music in the intensive care unit?. *The Southwest Respiratory and Critical Care Chronicles*, *4*(16), 40-44.

Chetty, S., Friedman, A. R., Taravosh-Lahn, K., Kirby, E. D., Mirescu, C., Guo, F., Krupik, D., Nicholas, A., Geraghty, A., Krishnamurthy, A., Tsai, M. K., Covarrubias, D., Wong, A., Francis, D., Sapolsky, R. M., Palmer, T. D., Pleasure, D., & Kaufer, D. (2014) Stress and

glucocorticoids promote oligodendrogenesis in the adult hippocampus. Molecular Psychiatry, 19(12), 1275–1283. https://doi.org/10.1038/mp.2013.190.

Chlan, L. L., Heiderscheit, A., Skaar, D. J., & Neidecker, M. V. (2018) Economic Evaluation of a Patient-Directed Music Intervention for ICU Patients Receiving Mechanical Ventilatory Support. Critical Care Medicine, 46(9), 1430–1435. https://doi.org/10.1097/CCM.0000000000003199

Chu, B., Marwaha, K., Sanvictores, T., & Ayers, D. (2021). Physiology, Stress Reaction. In StatPearls. StatPearls Publishing. Available online: https://www.ncbi.nlm.nih.gov/books/NBK541120/ (accessed on 13 November 2021)

Coburn D. (2018) Using MR to View PTSD's Effect on the Amygdala and Hippocampus. Radiologic technology, 89(5), 501–504.

Davydow, D. S., Desai, S. V., Needham, D. M., & Bienvenu, O. J. (2008) Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. Psychosomatic Medicine, 70(4), 512–519. https://doi.org/10.1097/PSY.0b013e31816aa0dd

Davydow, D. S., Gifford, J. M., Desai, S. V., Needham, D. M., & Bienvenu, O. J. (2008) Posttraumatic stress disorder in general intensive care unit survivors: a systematic review. General Hospital Psychiatry, 30(5), 421–434. https://doi.org/10.1016/j.genhosppsych.2008.05.006

de Witte, M., Spruit, A., van Hooren, S., Moonen, X., & Stams, G. J. (2020) Effects of music interventions on stress-related outcomes: a systematic review and two meta-analyses. Health Psychology Review, 14(2), 294–324. https://doi.org/10.1080/17437199.2019.1627897

Delgado, M. R., Nearing, K. I., Ledoux, J. E., & Phelps, E. A. (2008) Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. Neuron, 59(5), 829–838. https://doi.org/10.1016/j.neuron.2008.06.029

DellaVolpe, J. D., & Huang, D. T. (2015). Is there a role for music in the ICU? Critical Care (2016), 19. https://doi-org./10.1186/s13054-014-0663-1

Desai, R. (2019). Drug addiction. Available online: https://drrajivdesaimd.com/wp-content/uploads/2019/06/brain-and-drug-2.jpg (accessed on 13 November 2021).

Desai, S. V., Law, T. J., & Needham, D. M. (2011) Long-term complications of critical care. Critical Care Medicine 39(2), 371–379. https://doi.org/10.1097/CCM.0b013e3181fd66e5

Ding, Y., Zhang, Y., Zhou, W., Ling, Z., Huang, J., Hong, B., & Wang, X. (2019) Neural Correlates of Music Listening and Recall in the Human Brain. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 39(41), 8112–8123. https://doi.org/10.1523/JNEUROSCI.1468-18.2019

Dunlop, B. W., & Wong, A. (2019) The hypothalamic-pituitary-adrenal axis in PTSD: Pathophysiology and treatment interventions. Progress in neuro-psychopharmacology & biological psychiatry, 89, 361–379. https://doi.org/10.1016/j.pnpbp.2018.10.010

Ehlert, U., Gaab, J., & Heinrichs, M. (2001) Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamus-pituitary-adrenal axis. Biological Psychology, 57(1-3), 141–152. https://doi.org/10.1016/s0301-0511(01)00092-8

Etkin, A., & Wager, T. D. (2007) Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. The American journal of psychiatry, 164(10), 1476–1488. https://doi.org/10.1176/appi.ajp.2007.07030504

Ferrari, R. (2015) Writing narrative style literature reviews. Medical Writing, 24(4), 230-235. https://doi.org/10.1179/2047480615Z.000000000329

Finn, S., & Fancourt, D. (2018) The biological impact of listening to music in clinical and nonclinical settings: A systematic review. Progress in Brain Research, 237, 173–200. https://doi.org/10.1016/bs.pbr.2018.03.007

Flor, H., & Nees, F. (2014) Learning, memory, and brain plasticity in posttraumatic stress disorder: context matters. Restorative neurology and neuroscience, 32(1), 95–102. https://doi.org/10.3233/RNN-139013

Fuchs, E., & Flügge, G. (2014) Adult neuroplasticity: more than 40 years of research. Neural plasticity. Article 541870. https://doi.org/10.1155/2014/541870

Fukui, H., & Toyoshima, K. (2008) Music facilitates the neurogenesis, regeneration, and repair of neurons. Medical hypotheses, 71(5), 765–769. https://doi.org/10.1016/j.mehy.2008.06.019

Geretsegger, M., Elefant, C., Mössler, KA., Gold, C., (2014) Music therapy for people with autism spectrum disorder. Cochrane Database of Systematic Reviews, Issue 6. Art. No.: CD004381. https://doi.org/10.1002/14651858.CD004381.pub3.

Geretsegger, M., Mössler, K. A., Bieleninik, Ł., Chen, X. J., Heldal, T. O., & Gold, C. (2017) Music therapy for people with schizophrenia and schizophrenia-like disorders. The Cochrane Database of Systematic Reviews, 5(5), CD004025. https://doi.org/10.1002/14651858.CD004025.pub4

Gezginci, E., Goktas, S., & Orhan, B. N. (2020) The effects of environmental stressors in intensive care unit on anxiety and depression. Nursing in Critical Care, 10.1111/nicc.12553. https://doi.org/10.1111/nicc.12553

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., & Pitman, R. K. (2002) Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nature neuroscience, 5(11), 1242–1247. https://doi.org/10.1038/nn958

Gilbertson, M. W., Williston, S. K., Paulus, L. A., Lasko, N. B., Gurvits, T. V., Shenton, M. E., Pitman, R. K., & Orr, S. P. (2007) Configural cue performance in identical twins discordant for posttraumatic stress disorder: theoretical implications for the role of hippocampal function. Biological psychiatry, 62(5), 513–520. https://doi.org/10.1016/j.biopsych.2006.12.023

Girard, T. D., Shintani, A. K., Jackson, J. C., Gordon, S. M., Pun, B. T., Henderson, M. S., Dittus, R. S., Bernard, G. R., & Ely, E. W. (2007) Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. Critical Care (London, England), 11(1), R28. https://doi.org/10.1186/cc5708

Golden, T. L., Springs, S., Kimmel, H. J., Gupta, S., Tiedemann, A., Sandu, C. C., & Magsamen, S. (2021) The Use of Music in the Treatment and Management of Serious Mental Illness: A Global Scoping Review of the Literature. Frontiers in Psychology, 12, 649840. https://doi.org/10.3389/fpsyg.2021.649840

Griffiths, J., Fortune, G., Barber, V., & Young, J. D. (2007) The prevalence of post-traumatic stress disorder in survivors of ICU treatment: a systematic review. Intensive Care Medicine, 33(9), 1506–1518. https://doi.org/10.1007/s00134-007-0730-z

Grocke, D. E., & Wigram, T. (2007) Receptive methods in music therapy: techniques and clinical applications for music therapy clinicians, educators, and students. Jessica Kingsley Publishers.

Groussard, M., Viader, F., Landeau, B., Desgranges, B., Eustache, F., & Platel, H. (2014) The effects of musical practice on structural plasticity: the dynamics of grey matter changes. Brain and cognition, 90, 174–180. https://doi.org/10.1016/j.bandc.2014.06.013

Grupe, D. W., Hushek, B. A., Davis, K., Schoen, A. J., Wielgosz, J., Nitschke, J. B., & Davidson, R. J. (2019) Elevated perceived threat is associated with reduced hippocampal volume in combat veterans. Scientific Reports, 9(1), 14888. https://doi.org/10.1038/s41598-019-51533-x

Gullick, J. G., & Kwan, X. X. (2015) Patient-directed music therapy reduces anxiety and sedation exposure in mechanically ventilated patients: a research critique. Australian Critical Care: official journal of the Confederation of Australian Critical Care Nurses, 28(2), 103–105. https://doi.org/10.1016/j.aucc.2015.03.003

Gültekin, Y., Özçelik, Z., Akıncı, S. B., & Yorgancı, H. K. (2018) Evaluation of stressors in intensive care units. Turkish Journal of Surgery, 34(1), 5–8. https://doi.org/10.5152/turkjsurg.2017.3736

Guo, P., Li, Q., Wang, X., Li, X., Wang, S., Xie, Y., Xie, Y., Fu, Z., Zhang, X., & Li, S. (2020) Structural Covariance Changes of Anterior and Posterior Hippocampus During Musical Training in Young Adults. Frontiers in neuroanatomy, 14, 20. https://doi.org/10.3389/fnana.2020.00020)

Heiderscheit, A., Breckenridge, S. J., Chlan, L. L., & Savik, K. (2014) Music preferences of mechanically ventilated patients participating in a randomized controlled trial. *Music and medicine*, 6(2), 29–38. https://doi/10.47513/mmd.v6i2.177

Herman, J. P., McKlveen, J. M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., Scheimann, J., & Myers, B. (2016) Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress

Response. Comprehensive Physiology, 6(2), 603–621. https://doi.org/10.1002/cphy.c150015

Hetland, B., Lindquist, R., & Chlan, L. L. (2015) The influence of music during mechanical ventilation and weaning from mechanical ventilation: A review. Heart & Lung: The Journal of Critical Care, 44(5), 416–425. https://doi.org/10.1016/j.hrtlng.2015.06.010

Hole, J., Hirsch, M., Ball, E., & Meads, C. (2015) Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis. Lancet (London, England), 386(10004), 1659–1671. https://doi.org/10.1016/S0140-6736(15)60169-6

Jackson, J. C., Hart, R. P., Gordon, S. M., Hopkins, R. O., Girard, T. D., & Ely, E. W. (2007) Post-traumatic stress disorder and post-traumatic stress symptoms following critical illness in medical intensive care unit patients: assessing the magnitude of the problem. Critical Care (London, England), 11(1), R27. https://doi.org/10.1186/cc5707

Jackson, J. C., Pandharipande, P. P., Girard, T. D., Brummel, N. E., Thompson, J. L., Hughes, C. G., Pun, B. T., Vasilevskis, E. E., Morandi, A., Shintani, A. K., Hopkins, R. O., Bernard, G. R., Dittus, R. S., Ely, E. W., & Bringing to light the Risk Factors and Incidence of Neuropsychological dysfunction in ICU survivors (BRAIN-ICU) study investigators (2014) Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. The Lancet. Respiratory Medicine, 2(5), 369–379. https://doi.org/10.1016/S2213-2600(14)70051-7

Johnstone, T., van Reekum, C. M., Urry, H. L., Kalin, N. H., & Davidson, R. J. (2007) Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. The Journal of neuroscience: The official Journal of the Society for Neuroscience, 27(33), 8877–8884.

Khan, S. H., Kitsis, M., Golovyan, D., Wang, S., Chlan, L. L., Boustani, M., & Khan, B. A. (2018) Effects of music intervention on inflammatory markers in critically ill and post-operative patients: A systematic review of the literature. Heart & Lung: The Journal of Critical Care, 47(5), 489–496. https://doi.org/10.1016/j.hrtlng.2018.05.015

Kim, E. J., Pellman, B., & Kim, J. J. (2015) Stress effects on the hippocampus: a critical review. Learning & memory (Cold Spring Harbor, N.Y.), 22(9), 411–416. https://doi.org/10.1101/lm.037291.114

Kim, J. J., & Yoon, K. S. (1998) Stress: metaplastic effects in the hippocampus. Trends in neurosciences, 21(12), 505–509. https://doi.org/10.1016/s0166-2236(98)01322-8

Koelsch S. (2014) Brain correlates of music-evoked emotions. Nature reviews. Neuroscience, 15(3), 170–180. https://doi.org/10.1038/nrn3666

Koelsch S. (2020) A coordinate-based meta-analysis of music-evoked emotions. NeuroImage, 223, 117350. https://doi.org/10.1016/j.neuroimage.2020.117350

Koelsch, S. (2010) Towards a neural basis of music-evoked emotions. Trends in Cognitive Sciences, 14(3), 131–137. https://doi.org/10.1016/j.tics.2010.01.002

Koelsch, S. Emotion and Music. In J. Armony & P. Vuilleumier (Eds.), (2013) The Cambridge Handbook of Human Affective Neuroscience (pp. 286-303). Cambridge: Cambridge University Press. https://doi:10.1017/CBO9780511843716.016

Koelsch, S., & Skouras, S. (2014) Functional centrality of amygdala, striatum, and hypothalamus in a "small-world" network underlying joy: an fMRI study with music. Human brain mapping, 35(7), 3485–3498. https://doi.org/10.1002/hbm.22416

Koelsch, S., Fuermetz, J., Sack, U., Bauer, K., Hohenadel, M., Wiegel, M., Kaisers, U. X., & Heinke, W. (2011) Effects of Music Listening on Cortisol Levels and Propofol

Consumption during Spinal Anesthesia. Frontiers in Psychology, 2, 58. https://doi.org/10.3389/fpsyg.2011.00058

Koelsch, S., Skouras, S., Fritz, T., Herrera, P., Bonhage, C., Küssner, M. B., & Jacobs, A. M. (2013) The roles of superficial amygdala and auditory cortex in music-evoked fear and joy. NeuroImage, 81, 49–60. https://doi.org/10.1016/j.neuroimage.2013.05.008 [CD-recorded pieces from various epochs and styles

Laura S. Sakka, & Suvi Saarikallio. (2020) Spontaneous Music-Evoked Autobiographical Memories in Individuals Experiencing Depression. *Music & Science*, *3*. https://doi/10.1177/2059204320960575

Lee, M., Kang, J., & Jeong, Y. J. (2020) Risk factors for post-intensive care syndrome: A systematic review and meta-analysis. Australian Critical Care, 33(3), 287–294 https://doi.org/10.1016/j.aucc.2019.10.004

Liu, T., Ke, J., Qi, R., Zhang, L., Zhang, Z., Xu, Q., Zhong, Y., Lu, G., & Chen, F. (2021) Altered functional connectivity of the amygdala and its subregions in typhoon-related post-traumatic stress disorder. Brain & Behavior, 11(1), 1–15. https://doi-org /10.1002/brb3.1952

Lynch, K. A., Emard, N., Liou, K. T., Popkin, K., Borten, M., Nwodim, O., Atkinson, T. M., & Mao, J. J. (2021) Patient Perspectives on Active vs. Passive Music Therapy for Cancer in the Inpatient Setting: A Qualitative Analysis. Journal of pain and symptom management, , 62(1), 58–65. https://doi.org/10.1016

Maack, C. (2012) Outcomes and Processes of the Bonny Method of Guided Imagery and Music (GIM) and its Adaptations and Psychodynamic Imaginative Trauma Therapy (PITT) for Women with Complex PTSD. Thesis submitted for the degree of Doctor of Philosophy,

Aalborg University, Denmark,. https://vbn.aau.dk/ws/portalfiles/portal/68395912/Carola_Maack_12.pdf

Macfarlane, C., Masthoff, E., & Hakvoort, L. (2019) Short-Term Music Therapy Attention and Arousal Regulation Treatment (SMAART) for Prisoners with Posttraumatic Stress Disorder: A Feasibility Study. Journal of Forensic Psychology Research & Practice, 19(5), 376–392. https://doi/10.1080/24732850.2019.1670023

Magee, W. L., Clark, I., Tamplin, J., & Bradt, J. (2017) Music interventions for acquired brain injury. The Cochrane Database of Systematic Reviews, 1(1), CD006787. https://doi.org/10.1002/14651858.CD006787.pub3

Mary, A., Dayan, J., Leone, G., Postel, C., Fraisse, F., Malle, C., Vallée, T., Klein-Peschanski, C., Viader, F., de la Sayette, V., Peschanski, D., Eustache, F., & Gagnepain, P. (2020) Resilience after trauma: The role of memory suppression. *Science (New York, N.Y.)*, , *367*(6479), eaay8477. https://doi.org/10.1126/science.aay8477

Matsuo, K., Taneichi, K., Matsumoto, A., Ohtani, T., Yamasue, H., Sakano, Y., Sasaki, T., Sadamatsu, M., Kasai, K., Iwanami, A., Asukai, N., Kato, N., & Kato, T. (2003) Hypoactivation of the prefrontal cortex during verbal fluency test in PTSD: a near-infrared spectroscopy study. Psychiatry Research, 124(1), 1–10. https://doi.org/10.1016/s0925-4927(03)00093-3

Mavridis I. N. (2015) Music and the nucleus accumbens. Surgical and radiologic anatomy: SRA, 37(2), 121–125. https://doi.org/10.1007/s00276-014-1360-0

McAuley, M.T., Kenny, R.A., Kirkwood, T.B., Wilkinson, D.J., Jones, J.J., & Miller, V.M. (2009) A mathematical model of aging-related and cortisol induced hippocampal dysfunction. BMC Neurosci, 10(26). doi:10.1186/1471-2202-10-26

McFarlane A. C. (2010) The long-term costs of traumatic stress: intertwined physical and psychological consequences. World Psychiatry: Official Journal of the World Psychiatric Association (WPA), 9(1), 3–10. https://doi.org/10.1002/j.2051-5545.2010.tb00254

McGiffin, J. N., Galatzer-Levy, I. R., & Bonanno, G. A. (2016) Is the intensive care unit traumatic? What we know and don't know about the intensive care unit and posttraumatic stress responses. Rehabilitation Psychology, 61(2), 120–131. https://doi.org/10.1037/rep0000073

McKinney, C. H., & Honig, T. J. (2017) Health Outcomes of a Series of Bonny Method of Guided Imagery and Music Sessions: A Systematic Review. Journal of Music Therapy, 54(1), 1–34. https://doi.org/10.1093/jmt/thw016

Mclntosh, G. & Thaut, M. (2010). How music helps to heal the injured brain: Therapeutic use crescendos thanks to advances in brain science. The Dana Foundation. Available online: http://www.dana.org/Cerebrum/Default.aspx?id=39437 (accessed on 13 November 2021)

McNerney, M. W., Sheng, T., Nechvatal, J. M., Lee, A. G., Lyons, D. M., Soman, S., Liao, C. P., O'Hara, R., Hallmayer, J., Taylor, J., Ashford, J. W., Yesavage, J., & Adamson, M. M. (2018) Integration of neural and epigenetic contributions to posttraumatic stress symptoms: The role of hippocampal volume and glucocorticoid receptor gene methylation. PloS one, 13(2), e0192222. https://doi.org/10.1371/journal.pone.0192222

Mofredj, A., Alaya, S., Tassaioust, K., Bahloul, H., & Mrabet, A. (2016) Music therapy, a review of the potential therapeutic benefits for the critically ill. Journal of Critical Care, 35, 195–199. https://doi.org/10.1016/j.jcrc.2016.05.021.

Moore, K. S. (2013) A systematic review on the neural effects of music on emotion regulation: Implications for music therapy practice. *Journal of Music Therapy*, 50(3), 198-242. https://doi/doi:10.1093/jmt/50.3.198

Myers, B., McKlveen, J. M., & Herman, J. P. (2014) Glucocorticoid actions on synapses, circuits, and behavior: implications for the energetics of stress. Frontiers in neuroendocrinology, 35(2), 180–196. https://doi.org/10.1016/j.yfrne.2013.12.003

Needham, D. M., Davidson, J., Cohen, H., Hopkins, R. O., Weinert, C., Wunsch, H., Zawistowski, C., Bemis-Dougherty, A., Berney, S. C., Bienvenu, O. J., Brady, S. L., Brodsky, M. B., Denehy, L., Elliott, D., Flatley, C., Harabin, A. L., Jones, C., Louis, D., Meltzer, W., … Harvey, M. A. (2012) Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Critical Care Medicine. 40(2), 502–509. https://doi.org/10.1097/CCM.0b013e318232da75

Nickel, T. (2011). Trauma: HPA Axis [Video]. Available online: https://www.youtube.com/watch?v=otLHMbNyUx0 (accessed on 13 November 2021)

Olszewska, A. M., Gaca, M., Herman, A. M., Jednoróg, K., & Marchewka, A. (2021) How Musical Training Shapes the Adult Brain: Predispositions and Neuroplasticity. Frontiers in neuroscience, 15, 630829. https://doi.org/10.3389/fnins.2021.630829

Parada-Cabaleiro, E., Batliner, A., & Schedl, M. (2022) An Exploratory Study on the Acoustic Musical Properties to Decrease Self-Perceived Anxiety. *International journal of environmental research and public health*, 19(2), 994. https://doi.org/10.3390/ijerph19020994

Parker, A. M., Sricharoenchai, T., Raparla, S., Schneck, K. W., Bienvenu, O. J., & Needham, D. M. (2015) Posttraumatic stress disorder in critical illness survivors: a metaanalysis. Critical Care Medicine. 43(5), 1121–1129. https://doi.org/10.1097/CCM.0000000000000882

Perkins, R., Mason-Bertrand, A., Fancourt, D., Baxter, L., & Williamon, A. (2020) How Participatory Music Engagement Supports Mental Well-being: A Meta-Ethnography. Qualitative Health Research, 30(12), 1924–1940. https://doi.org/10.1177/1049732320944142

Postel, C., Mary, A., Dayan, J., Fraisse, F., Vallée, T., Guillery-Girard, B., Viader, F., Sayette, V., Peschanski, D., Eustache, F., & Gagnepain, P. (2021) Variations in response to trauma and hippocampal subfield changes. Neurobiology of Stress, 15, 100346. https://doi.org/10.1016/j.ynstr.2021.100346

Pourmovahed, Z., Yassini Ardekani, S. M., Roozbeh, B., & Ezabad, A. R. (2021) The Effect of Non-verbal Music on Posttraumatic Stress Disorder in Mothers of Premature Neonates. Iranian Journal of Nursing and Midwifery Research, 26(2), 150–153. https://doi.org/10.4103/ijnmr.IJNMR_37_20

Rabiee, A., Nikayin, S., Hashem, M. D., Huang, M., Dinglas, V. D., Bienvenu, O. J., ... & Needham, D. M. (2016) Depressive symptoms after critical illness: a systematic review and meta-analysis. Critical Care Medicine, 44(9), 1744-1753. doi:10.1097/CCM.0000000000001811.

Reybrouck, M., Vuust, P., & Brattico, E. (2018) Music and brain plasticity: how sounds trigger neurogenerative adaptations. Neuroplasticity Insights of Neural Reorganization, 85. http://doi.org/10.5772/intechopen.74318

Righy, C., Rosa, R. G., da Silva, R., Kochhann, R., Migliavaca, C. B., Robinson, C. C., Teche, S. P., Teixeira, C., Bozza, F. A., & Falavigna, M. (2019) Prevalence of post-traumatic stress disorder symptoms in adult critical care survivors: a systematic review and meta-analysis. Critical care (London, England), 23(1), 213. https://doi.org/10.1186/s13054-019-2489-3

Rousseau, A. F., Prescott, H. C., Brett, S. J., Weiss, B., Azoulay, E., Creteur, J., Latronico, N., Hough, C. L., Weber-Carstens, S., Vincent, J. L., & Preiser, J. C. (2021) Long-term outcomes after critical illness: recent insights. Critical Care (London, England), 25(1), 108. https://doi.org/10.1186/s13054-021-03535-3

Rudstam, G., Elofsson, U., Søndergaard, H. P., & Beck, B. D. (2017) Trauma-focused group music and imagery with women suffering from PTSD/complex PTSD: a feasibility study. Approaches. Music Therapy and Special Education, 9(2), 202-216.

Schaefer H. E. (2017) Music-Evoked Emotions-Current Studies. Frontiers in neuroscience, 11, 600. https://doi.org/10.3389/fnins.2017.00600

Schoenfeld, T. J., & Gould, E. (2012) Stress, stress hormones, and adult neurogenesis. Experimental Neurology, 233(1), 12–21. https://doi.org/10.1016/j.expneurol.2011.01.008

Selemon, L. D., Young, K. A., Cruz, D. A., & Williamson, D. E. (2019) Frontal Lobe Circuitry in Posttraumatic Stress Disorder. Chronic Stress. https://doi.org/10.1177/2470547019850166

Sheerin, C. M., Lind, M. J., Bountress, K. E., Marraccini, M. E., Amstadter, A. B., Bacanu, S. A., & Nugent, N. R. (2020) Meta-Analysis of Associations Between Hypothalamic-Pituitary-Adrenal Axis Genes and Risk of Posttraumatic Stress Disorder. Journal of traumatic stress, 33(5), 688–698. https://doi.org/10.1002/jts.22484

Sherin, J. E., & Nemeroff, C. B. (2011) Post-traumatic stress disorder: the neurobiological impact of psychological trauma. Dialogues in Clinical Neuroscience, 13(3), 263–278

Smith M. E. (2005) Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: a meta-analysis of structural MRI studies. Hippocampus, 15(6), 798–807. https://doi.org/10.1002/hipo.20102

Stevens, J. S., Jovanovic, T., Fani, N., Ely, T. D., Glover, E. M., Bradley, B., & Ressler, K. J. (2013) Disrupted amygdala-prefrontal functional connectivity in civilian women with posttraumatic stress disorder. Journal of Psychiatric Research, 47(10), 1469–1478. https://doi.org/10.1016/j.jpsychires.2013.05.031

Story, K. M. & Beck, B. D. (2017) Guided Imagery and Music with female military veterans: An intervention development study. Arts in Psychotherapy, 55, 93–102. https://doi-org/10.1016/j.aip.2017.05.003

Stress and the brain. Available online: https://turnaroundusa.org/wp-content/uploads/2020/03/Stress-and-the-Brain_Turnaround-for-Children-032420.pdf (accessed on 13 November 2021)

Tan, X., Yowler, C. J., Super, D. M., & Fratianne, R. B. (2012) The interplay of preference, familiarity and psychophysical properties in defining relaxation music. *Journal of Music Therapy*, 49(2), 150-179. https://doi/doi:10.1093/jmt/49.2.150

Umbrello, M., Sorrenti, T., Mistraletti, G., Formenti, P., Chiumello, D., & Terzoni, S. (2019) Music therapy reduces stress and anxiety in critically ill patients: a systematic review of randomized clinical trials. Minerva Anestesiologica, 85(8), 886–898. https://doi /10.23736/S0375-9393.19.13526-2

Urry, H. L., van Reekum, C. M., Johnstone, T., Kalin, N. H., Thurow, M. E., Schaefer, H. S., Jackson, C. A., Frye, C. J., Greischar, L. L., Alexander, A. L., & Davidson, R. J. (2006) Amygdala, and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. The Journal of neuroscience: The Official Journal of the Society for Neuroscience, 26(16), 4415–4425. https://doi.org/10.1523/JNEUROSCI.3215-05.2006

van der Steen, J. T., van Soest-Poortvliet, M. C., van der Wouden, J. C., Bruinsma, M. S., Scholten, R. J., & Vink, A. C. (2017) Music-based therapeutic interventions for people with dementia. The Cochrane Database of Systematic Reviews, 5(5), CD003477. https://doi.org/10.1002/14651858.CD003477

van Rooij, S. J. H., Kennis, M., Sjouwerman, R., van den Heuvel, M. P., Kahn, R. S., & Geuze, E. (2015) Smaller hippocampal volume as a vulnerability factor for the persistence of post-traumatic stress disorder. Psychological Medicine, 45(13), 2737–2746. https://doi /10.1017/S0033291715000707

Wade, D. F., Moon, Z., Windgassen, S. S., Harrison, A. M., Morris, L., & Weinman, J. A. (2016) Non-pharmacological interventions to reduce ICU-related psychological distress: a systematic review. Minerva Anestesiologica, 82(4), 465–478.)

Wade, D., Hardy, R., Howell, D., & Mythen, M. (2013) Identifying clinical and acute psychological risk factors for PTSD after critical care: a systematic review. Minerva Anestesiologica, 79(8), 944–963.

Wang, S., & Agius, M. (2018) The use of Music Therapy in the treatment of Mental Illness and the enhancement of Societal Wellbeing. Psychiatria Danubina, 30(Suppl 7), 595–600.

Wang, Z., Neylan, T. C., Mueller, S. G., Lenoci, M., Truran, D., Marmar, C. R., Weiner, M. W., & Schuff, N. (2010) Magnetic resonance imaging of hippocampal subfields in posttraumatic stress disorder. Archives of General Psychiatry, 67(3), 296–303. https://doi.org/10.1001/archgenpsychiatry.2009.205

Warner-Schmidt, J. L., & Duman, R. S. (2006) Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. Hippocampus, 16(3), 239–249. https://doi.org/10.1002/hipo.20156

Wintermann, G.-B., Brunkhorst, F. M., Petrowski, K., Strauss, B., Oehmichen, F., Pohl, M., & Rosendahl, J. Stress disorders following prolonged critical illness in survivors of severe sepsis. Critical Care Medicine (2015), 43(6), 1213–1222. https://doi.org/10.1097/CCM.0000000000000936

Xiong, K., Zhang, Y., Qiu, M., Zhang, J., Sang, L., Wang, L., Xie, B., Wang, J., & Li, M. (2013) Negative emotion regulation in patients with posttraumatic stress disorder. PloS one, 8(12), e81957. https://doi.org/10.1371/journal.pone.0081957

Xu, B., Sui, Y., Zhu, C., Yang, X., Zhou, J., Li, L., Ren, L., & Wang, X. (2017) Music intervention on cognitive dysfunction in healthy older adults: a systematic review and meta-analysis. Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 38(6), 983–992. https://doi.org/10.1007/s10072-017-2878-9

Yinger, O. S., & Gooding, L. F. (2015) A systematic review of music-based interventions for procedural support. *Journal of music therapy*, 52(1), 1–77. https://doi.org/10.1093/jmt/thv004

Zatorre R. J. (2015) Musical pleasure and reward: mechanisms and dysfunction. Annals of the New York Academy of Sciences, 1337, 202–211. https://doi.org/10.1111/nyas.12677

Zengin, N., Ören, B., & Üstündag, H. (2020) The relationship between stressors and intensive care unit experiences. Nursing in Critical Care, 25(2), 109–116. https://doi.org/10.1111/nicc.12465

Zergani, E. J., & Naderi, F. (2016) The Effectiveness of Music on Quality of Life and Anxiety Symptoms in the Post Traumatic Stress Disorder in Bustan Hospital of Ahvaz City. Review of European Studies, 8(3), 237–243. https://doi.org/10.5539/res.v8n3p237

Manuscript II

Screening Tools for Post-Intensive Care Syndrome and Post-traumatic Symptoms in ICU Survivors: A Scoping Review

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Screening Tools for Post-Intensive Care Syndrome and Post-traumatic Symptoms in ICU Survivors: A Scoping Review

Abstract

Background: Evidence suggests that ICU survivors often suffer long-term complications such as PICS and PTSD from critical illness and ICU stay. PICS and PTSD not only affect ICU survivors, but also their families and dramatically increases costs for healthcare systems. The current lack of evidence on the comparative psychometric properties of the assessment tools is a major barrier in evidence-based screening for post-ICU symptomatology and health related quality of life. **Objectives:** We aimed to identify existing tools for screening of PTSD and PICS in ICU survivors and their families, and to examine evidence on the validity, reliability, sensitivity, and specificity of existing tools, as reflected in published peer-reviewed studies. **Method:** A scoping review based on literature searches [CINAHL, MEDLINE, EMBASE, PsycINFO, Scopus, Health and Psychosocial Instruments, Dissertations and Theses Global and Google Scholar], and predefined eligibility criteria was conducted according to current scoping review guidelines. **Findings:** We identified 44 studies reporting on the development and assessment of psychometric properties of PICS/PTSD in ICU survivors or families globally. We identified 5 tools addressing all 3 aspects of PICS manifestations (physical, psychological, cognitive), 1 tool for both physical and mental aspects of PICS, and 5 tools for quality-of-life assessment in ICU survivors. Altogether, 25 tools assess only one aspect of PICS: 5 for cognitive impairment, 7 for physical impairment, and 13 for mental health impairment and PTSD in ICU survivors. However, only 2 tools were found for PICS-family assessment. Other findings include: a) unclear validity and often limited feasibility of tools, b) low diagnostic accuracy of cognitive assessment tools, and c) evidence of appropriate psychometric properties and feasibility of psychological health assessment tools. **Conclusion:**

These results have implications for the selection and implementation of the assessment methods as a means for promoting meaningful patient-centered clinical outcomes to minimize long-term sequelae, reduce the rate of re-hospitalization, and optimize recovery after ICU discharge.

Keywords: Assessment tool, ICU Survivors, PICS, PTSD, reliability, validity

Introduction

Ongoing advancements in Intensive Care Unit (ICU) technology and evidence-based practice have significantly reduced ICU related mortality. However, most ICU survivors do not return to their prior state of health, even years after critical illness (Annachiara et al., 2018; Desai et al., 2011; Needham et al., 2012). Evidence suggests that ICU survivors often suffer noteworthy long-term complications from critical illness and ICU stay (Oeyen et al., 2010). These involve a constellation of physical impairments, altered cognition and development of neuropsychiatric symptoms (Desai et al., 2011; Rawal et al., 2017; Rousseau et al., 2021; Yuan et al., 2021), which have been termed post-intensive care syndrome (PICS). Furthermore, one in three ICU survivors exhibit clinically significant symptoms of depression or post-traumatic stress disorder (PTSD) in the first year after ICU stay (Parker et al., 2015; Rabiee et al., 2016); among which, clinically significant symptoms of PTSD are evident in 19.83% (Righy et al., 2019). However, point prevalence estimates were 15.93%, 16.80%, 18.96%, and 20.21% at 3, 6, 12, and > 12 months post discharge, respectively (Righy et al., 2019). Critical illness can profoundly impact the quality of life of patients' families, which is termed as PICS-F (Davidson et. al., 2012; Needham et al., 2012). PICS-F is prevalent in 48% of family members comprised of 13% depression, 29% anxiety, and 39% PTSD, among which 33% require serious medical assistance for anxiety or depression (Davidson et al., 2012; Harlan et al., 2020; Jezierska, 2014).

Recently, there is an increased emphasis on preventive and therapeutic approaches for ICU-related PICS and PTSD (Amra et al., 2018; Appleton et al., 2015; Wade et al., 2016). Early identification and initiation of treatment have been shown to improve patient outcomes (Lasiter et al., 2016; McIlroy et al., 2019; Wade et al., 2016). Thus, valid and reliable screening tools are vital for early detection and evaluation of the intervention outcomes. Despite the use of several tools,

there is no gold standard or guideline available for the assessment of ICU-related PTSD/PICS (American Psychological Association, 2017; Needham et al., 2012; Umberger, 2019). Lack of evidence on the comparative psychometric properties of the assessment tools is a major barrier in evidence-based screening. Systematic reviews of risk factors, incidence rates, and interventions for PTSD and PICS in ICU survivors as well as family are available, but so far, none have assessed the psychometric properties of assessment tools. Therefore, this review aims to address the gap by synthesizing evidence of the characteristics and psychometric properties of available assessment tools for PTSD and PICS in ICU survivors and their families.

Purpose & Objectives

The purpose of this scoping review is to synthesize evidence on tools assessing PTSD and PICS in ICU survivors and their families. Specific objectives included to:

1. Identify existing tools for screening of PTSD and PICS in ICU survivors and their families,
2. Examine evidence on the validity, reliability, sensitivity, and specificity of existing tools, as reflected in published peer-reviewed studies, and
3. Identify current uses of the identified tools (i.e., screening, diagnostic, research).

Methods

The review was directed by a protocol based on current guidance for scoping reviews (Levac et al., 2010). Reporting was guided by Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018). The research question that guided the scoping review was “What are the properties, scope, and uses of tools available for the assessment of PTSD and PICS in ICU survivors and their family or caregivers?”

Eligibility criteria

Inclusion criteria: (a) peer-reviewed studies reporting on the development or modification of tools/scales/questionnaires to assess PICS and PTSD in ICU survivors and their families irrespective of type of ICU setting, and patients' background characteristics (diagnosis, treatment, age); b) studies involving adult participants post-ICU hospitalization; and (c) peer reviewed studies reporting on applications and/or testing the psychometric properties of existing tools/scales/questionnaires on PICS and PTSD in ICU survivors and their families irrespective of type of ICU setting, and patients' background characteristics.

Exclusion criteria: a) studies addressing patients under 18 years of age; b) secondary analyses, reviews, books, book chapters, commentaries, editorials, letters and other non-primary source types, opinion papers; c) articles in any language other than English.

Information sources and search strategy

A systematic literature search was conducted in February 2021 and repeated in March 2022 with the help of an experienced health sciences librarian to identify all relevant published studies. Searches were performed in the following databases: MEDLINE via OVID, EMBASE via OVID, PsycINFO via OVID, Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus with Full Text via EBSCOhost, Scopus via Elsevier, Health and Psychosocial Instruments (HAPI) via OVID, and Dissertations and Theses Global via ProQuest.

We employed a combination of natural language vocabulary and controlled terms. Natural language terms were derived from two main concepts: a) Tools for PICS/PICS-F/PTSD/PTSD-F assessment and b) ICU survivors. Additionally, we employed an ancestry and descendancy approach, using Scopus, of the papers to be synthesized in the review. To increase the sensitivity

of the search, publication dates were not applied. The search strategy used in MEDLINE and CINAHL is included in appendix (S1).

Selection of sources of evidence and data charting

Search outcomes were exported into Covidence for data management, removal of duplicates and independent screening for inclusion. Two team members (UP and SM) independently screened titles and abstracts of search outcomes for eligibility, and conflicts were resolved with a third reviewer (EP). An article was passed on to the next stage of full-text screening only when it appeared relevant to the topic understudy. Inter-rater reliability was achieved through the mutuality of agreement made on the type of studies to be included. A data charting tool was iteratively developed by the research team and pilot tested on the first five articles to ensure all required data was captured.

Quality assessment

Quality of studies reporting on the diagnostic reliability of tools was assessed with the Quality Appraisal of Diagnostic Reliability checklist (QAREL) (Lucas et al., 2010). The process was iterative and continued until consensus among 3 raters (UP, KV and EP) was achieved.

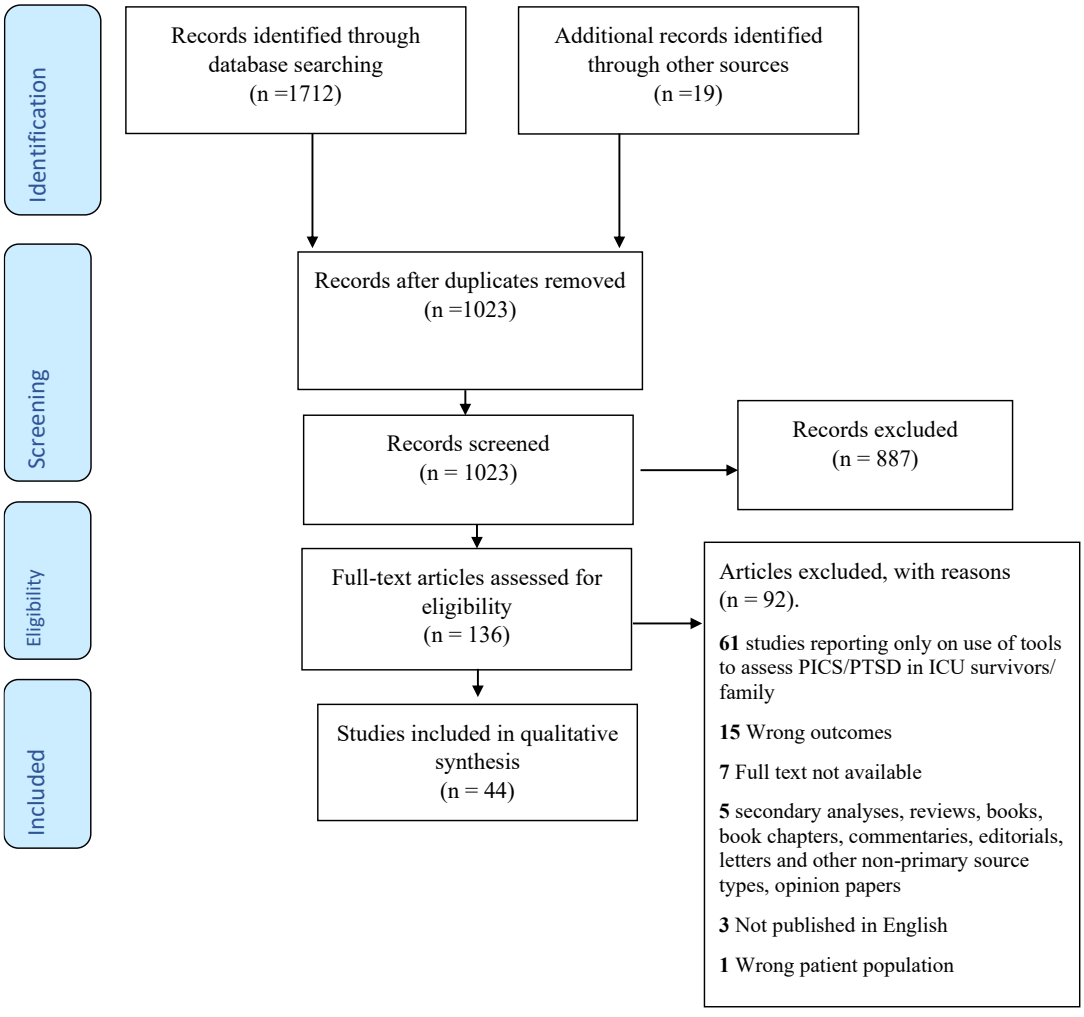
Results

Study characteristics

Overall, 1712 studies were retrieved from databases, and after removing duplicates, 1023 titles and abstracts were screened for inclusion. Of these studies, 887 were excluded as irrelevant and 136 papers were further examined based on the eligibility criteria. We finally identified 44 studies reporting on development and assessment of psychometric properties of PICS/PTSD in ICU survivors or families globally (Fig. 1). Most of the studies (n=11) were conducted in the United States; seven each in the United Kingdom and Sweden; five in Germany; three in the Netherlands;

two in both Korea and Morocco; and one each conducted in Cyprus, France, Finland, Canada, and Brazil. Additionally, 3 studies were multinational: 2 studies in Sweden, Denmark, and the Netherlands, and 1 study in United States and Australia. Study designs were mostly prospective cohort, observational, or cross-sectional focusing on instrument development and/or validation (Table 1). Most of the identified studies used either purposive or convenience sampling from the following sites: medical, surgical, neurosurgical, cardiovascular, trauma or mixed/general ICUs. However, 2 studies included ICU survivors from rehabilitation hospitals (Wintermann et al., 2018) and long-term acute care hospitals (Jubran, et al., 2010).

Figure 1: PRISMA CHART FOR SCOPING REVIEW



Scope of identified tools

Most tools were either developed or adapted by the authors specifically for ICU survivors or family caregivers using evidence-informed approaches, such as literature reviews, expert consultations, and pilot testing. The identified tools addressed various aspects of the psychological, physical, and cognitive health of ICU survivors or their families and were based on patient-reported ratings.

Tools for PICS

A total of five tools – Provisional Questionnaire for Long-Term Health-Related Quality of Life and Burden of Disease After Intensive Care (Malmgren, et al., 2021), Healthy Aging Brain Care-Monitor Self Report (HABC-M SR) (Wang, et al., 2019), set of Outcome Measurement Instruments (OMI set) (Spies, et al., 2019), Post-Intensive Care Syndrome Questionnaire (PICS-Q) (Jeong, et al., 2019; Kang, et al., 2020), and Recovery After INtensive care (RAIN) (Bergbom, et al., 2018) – addressed all aspects of PICS in ICU survivors. However, the 3-Set 4P questionnaire addressed only two major aspects of PICS: physical and psychosocial (Akerman, et al., 2009; Akerman, et al., 2012). Moreover, four tools were non-specific for PICS or PTSD and addressed health-related quality of life in ICU survivors: 36-Item Short Form (SF-36) (Chrispin, et al., 1996), Sickness Impact Profile (SIP) (Tian and Miranda, 1994), Perceived Quality of Life Scale (PQOL) (Patrick et al., 1988), Arabic and Finnish versions of the EuroQol 5 Dimensions (EQ-5D) (Kaarlola et al., 2004; Khoudri, et al., 2012), the Finnish version of RAND 36-Item Health Survey (RAND-36) (Kaarlola et al., 2004), and the Arabic version of SF-36. The RAND 36-Item Health Survey includes the same items as those in the SF-36, but with a different scoring algorithm.

Tools for Cognitive Impairments

Altogether, 25 tools were identified that assessed only one aspect of PICS. Among which, five tools addressed only cognitive aspects in ICU survivors: 14-item Cognitive Failure Questionnaire (CFQ-14) (Wassenaar et al., 2018), 26-item Mini-Mental State Examination (MMSE-26) (Pfoh et.al 2015), Montreal Cognitive Assessment Tool (MoCA) (Brown et al, 2018), the German version of Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog $_{\text{adapted}}$) (Baumbach et al., 2016), and telephone battery (Christie et al, 2006).

Tools for Physical Impairments

Additionally, seven tools addressed the physical aspect of PICS alone in ICU survivors: ICU discharge screening tool for prediction of new-onset physical disability (Milton et al.,2019), Multidimensional Fatigue Inventory (MFI-20) (Wintermann et al., 2018), the predictive screening instrument (Schandl 2014), Chelsea Critical Care Physical Assessment tool (CPAx) (Corner et al., 2012; Corner et al., 2014), Barthel Index (BI) and Katz Index (KI) (Da Silveira et al., 2018), and 6-Min Walk Distance (6MWD) (Chan et al., 2015).

Tools for Mental Health Impairments & PTSD

Psychological aspects of PICS were addressed by four tools: Depression, Anxiety, and Stress Scale (DASS) (Sukantarat et al., 2007); Hospital Anxiety and Depression scale (HADS) (Jutte et al., 2015; Milton et al., 2017); the psychological risk prediction instrument for use at ICU discharge (Milton et al., 2018); and the predictive screening instrument (Schandl et al., 2013). In addition, eight tools addressed PTSD in ICU survivors: 10-item Post-Traumatic Stress Syndrome questionnaire (PTSS-10) (Jubran, et al., 2010; Milton et al., 2017; Nickel, et al., 2004; Rosendahl, et., 2019; Stoll, et al., 1999),14-item Post-Traumatic Stress Syndrome (PTSS-14) (Rosendahl, et., 2019; Warlan, et al., 2016), Posttraumatic Stress Disorder Checklist (PCL-5) (Rosendahl, et., 2019), UK Post-Traumatic Stress Syndrome 14-Questions Inventory (UK-PTSS-14) (Twigg, et

al., 2008), 22-item Impact of Event Scale-Revised (IES-R) (Bienvenu, et al., 2013), Impact of Event Scale 6 (IES-6) (Hosey, et al., 2019), Experience after Treatment in Intensive Care 7-Item Scale (ETIC-7) (Scragg, et al.,2000), and the Cypriot version of DTS-I-M (CDTS-I-T) (Karanikola, et al., 2020). Additionally, one item on one tool, the sleep item on the PTSD Checklist – Civilian version (PCL-C sleep item) (Parsons, et al., 2018), was identified that assessed insomnia among the ICU survivors.

Tools for PICS- Family

Only two studies addressed family caregivers. Among which, CAESAR addressed PTSD in families of patients who died in the ICU (Kentish-Barnes et al., 2016), and the German version of Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog $_{adapted}$), addressed cognitive health in families of ICU survivors (Baumbach et al., 2016).

Mean age of the ICU survivors was 38.2-77 years (range 18-90 years). Whereas median age for family caregiver was 56.5 years (range 18-85 years). The sample size varied from 30-3665 participants. Only a few studies (n=10) used sample sizes below 50 (Akerman, et al., 2009; Brown et.al, 2018; Christie et.al, 2006; Corner et al., 2012; Heyland et.al., 2000; Jubran, et al., 2010; Nickel, et al., 2004; Spies, et al., 2019; Twigg, et al., 2008; Warlan, et al., 2016) probably limiting statistical power.

Most studies assessed PICS/PTSD in survivors of general or mixed ICUs. Of the identified studies, two studies included ICU survivors who were treated with invasive mechanical ventilation (IMV) for at least 24 hours (Da Silveira et al., 2018; Jubran, et al., 2010). Furthermore, six studies assessed PICS/PTSD in survivors of acute respiratory distress syndrome (ARDS) (Bienvenu, et al., 2013; Chan et al., 2015; Christie et.al, 2006; Hosey, et al., 2019; Jutte et al., 2015; Stoll, et al.,

1999), and three papers focused on sepsis survivors (Brown et al, 2018; Heyland et al., 2000; Rosendahl et., 2019).

Most of the included studies reported gender/sex of the participants. Most of the samples comprised of significantly more male (>60%) than female participants (Akerman, et al., 2012; Bergbom et al., 2018; Baumbach et al., 2016; Chrispin et al., 1996; Chan et al., 2015; Corner et al., 2012; Jeong, et al., 2019; Jiyeon et al., 2020; Jubran et al., 2010; Kaarlola et al., 2004; Karanikola et al., 2020;Malmgren et al., 2021; Milton et al.,2019; Milton et al., 2018; Nickel et al., 2004; Rosendahl et., 2019; Schandl, 2014; Spies et al., 2019; Warlan, et al., 2016; Wassenaar et al 2018; Wintermann et al., 2018).

Few studies assessed the validity and reliability of the tools without reference to a 'gold standard' (Bergbom et al., 2018; Corner et al., 2014; Chrispin 1996; Kang, et al., 2020; Malmgren, et al., 2021; Milton et al., 2017; Tian and Miranda, 1994). A reference score was employed in most studies for validation purposes (Table 1). Tools most often employed as a gold standard for PICS were the 36- or 12-item Short Form questionnaires (Akerman et al., 2009; Akerman et al., 2012; Jeong et al., 2019). Similarly, tools most often employed as 'gold standard' for PTSD were the Structured Clinical Interview (SCID), Clinician-Administered PTSD Scale (CAPS) and PTSD Checklist – Civilian version (PCL-C) (Bienvenu et al., 2013; Hosey et al., 2019; Jubran et al., 2010; Nickel et al., 2004; Rosendahl et al., 2019; Stoll et al., 1999; Warlan et al., 2016).

Table 1: Summary of the identified studies

Author & Date	**Context**	**Name of Tool**	**Aim of the Study**	**Study design**	**Patient population and Sample size**	**Sample characteristics**
Tools for PICS Assessment						
Akerman et al., 2009	***Country:*** Sweden ***Site:*** Two mixed med-surg ICUs	3-Set 4P questionnaire	Develop and evaluate the validity and reliability of a	***Overall study design:*** Not reported	***Target population:*** ICU survivors	***Mean Age:*** 60.3 (±14.6) years ***Gender/Sex:*** 21 (54%) males

			questionnaire for assessing physical and psychosocial problems over time for patients following ICU recovery.	***Sampling method:*** Convenience sampling ***Timing of Assessment:*** 2-, 6-, or 12-months post-ICU discharge ***Reference Score:*** SF-12	***# of participants:*** 39 and retested in only 17 participants	
Akerman et al., 2012	***Country:*** Sweden ***Site:*** Four general ICUs	3-Set 4P questionnaire	Psychometrically test and evaluate the 3-set 4P questionnaire in a larger population.	***Overall study design:*** Not reported ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** Two months after discharge ***Reference Score:*** SF-36	***Target population:*** ICU survivors ***# of participants:*** 421	***Mean Age:*** 68 years (±15) ***Gender/Sex:*** 254 (60%) males
Malmgren et al., 2021	***Country:*** Sweden ***Site:*** Mixed ICUs	Provisional questionnaire for long-term health-related quality of life and burden of disease after intensive care (Name not given).	Construct a provisional questionnaire on health-related issues based on interviews with ICU survivors and to test if this questionnaire was able to show differences between ICU survivors and non-ICU-treated controls.	***Overall study design:*** Mixed method ***Sampling method:*** Purposive sampling ***Timing of Assessment:*** 6 months to 3 years after discharge ***Reference Score:*** None	***Target population:*** ICU survivors ***# of participants: Interview population:*** 32 ***Test population:*** 592 (395 ICU survivors and 197 controls)	***Median age:*** *Interview population*: 55.5 (range 20-80) years *Test population:* 65 years (SD=18) ***Gender/Sex:*** *Interview population:* 33% female *Test population:* ICU survivors: 239 (61%) males Controls: 117 (60%) males
Wang et al., 2019	***Country:*** United States ***Site:*** Critical Care Recovery Center at Eskenazi Hospital	Healthy Aging Brain Care-Monitor Self Report (HABC-M SR)	Validate face to face administration of the HABC-M SR as a rapid assessment tool for PICS.	***Overall study design:*** Not reported ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** Within a week of initial visit ***Reference Score:*** RABINS, CERAD-NB, GDS-30, PHQ-9, PTSS-10, PSMS	***Target population:*** ICU survivors ***# of participants:*** 142	**Mean Age**: 52.3 years (SD=13.0) ***Gender/ Sex:*** 48% female

Spies et al., 2019	***Country:*** Germany ***Site:*** Mixed ICU (Charite´ – Universita¨ tsmedizin Berlin AND Brandenburg Clinic in Bad Belzig)	Set of outcome measurement instruments (OMI set)	Propose a set of outcome measurement instruments (OMIs) to measure PICS in settings of outpatient healthcare service as well as a feasibility assessment of these OMIs.	***Overall study design:*** Not reported ***Sampling method:*** Convenience Sampling ***Timing of Assessment:*** Not reported ***Reference Score:*** None	***Target population:*** ICU survivors ***# of participants:*** *Feasibility testing: Preliminary Set 1*: 5 *Feasibility testing: Preliminary Set 2*: 5 *Feasibility testing: Final set*: 4	***Mean Age:*** *Feasibility testing: Preliminary Set 1*= 77 years (range 53-82) *Feasibility testing: Preliminary Set 2*= 77 years (range 53-82) *Feasibility testing: Final set*= 45.5 years (range 23-56) ***Gender/Sex:*** *Feasibility testing: Preliminary Set 1*- 60% male *Feasibility testing: Preliminary Set 2*- 60% male *Feasibility testing: Final set*- 50% male
Jeong et al., 2019	***Country:*** Korea ***Site:*** mixed ICUs (7 health care facilities in three cities of Korea)	Post-Intensive Care Syndrome Questionnaire (PICSQ)	Develop a Post-Intensive Care Syndrome Questionnaire (PICSQ) and assess the psychometric properties of PICSQ in intensive care unit survivors.	***Overall study design:*** Not reported ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** 4 weeks to one-year post-discharge ***Reference Score:*** JFS, SF-36	***Target population***: ICU survivors ***# of participants:*** 536	***Mean Age***: 57.0 years (SD=14.5) ***Gender/Sex:*** 56.2% male 34.8% female
Kang et al., 2020	***Country:*** Korea ***Site:*** Not reported (participants were admitted to: Surgical, neurologic, cardiovascular, and medical ICUs)	Post-Intensive Care Syndrome Questionnaire (PICSQ)	Assign weights for subscales and items of the Post-Intensive Care Syndrome questionnaire and suggest optimal cut-off values for screening unplanned hospital readmissions of critical care survivors.	***Overall study design:*** Cross-sectional design ***Sampling method:*** Voluntary response sampling ***Timing of Assessment:*** < 1-year post-discharge ***Reference Score:*** *None*	***Target population:*** ICU survivors ***# of participants:*** 240	***Mean Age:*** 61.4 years (SD=14.54) ***Gender/Sex:*** 70.8% male
Bergbom et al., 2018	***Country:*** Sweden ***Site:*** General ICU (surgical, medical and trauma)	Recovery After INtensive care (RAIN)	Development and evaluation of the Recovery after Intensive Care questionnaire's	***Overall study design:*** Not reported ***Sampling method:*** Convenience sampling	***Target population:*** ICU survivors ***# of participants:*** 169	***Mean Age:*** 69 years (SD=12.5) ***Gender/Sex:*** 103 (61%) males 66 (39%) females

			(RAIN) validity and reliability.	***Timing of Assessment:*** 2-, 6-, 12-, or 24-months post-discharge ***Reference Score:*** None		
Chrispin et al., 1996	***Country:*** United Kingdom ***Site:*** General ICU (Norfolk and Norwich Hospital)	36-Item Short Form (SF-36)	Assess the acceptability, validity, and reliability of the Short Form 36 quality of life questionnaire in adult patients following discharge from a general intensive care unit.	***Overall study design:*** Not reported ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** "Just prior to discharge from ICU" ***Reference Score:*** None	***Target population:*** Adult ICU survivors ***# of participants:*** 166	***Median Age:*** 61.9 years (range 59.0-64.2) ***Gender/Sex:*** 113 males 53 females
Tian and Miranda, 1994	***Country:*** Netherlands ***Site:*** 36 Dutch ICUs	Sickness Impact Profile (SIP)	Validate the structure of the Sickness Impact Profile scale (SIP) when applied to intensive care patients after discharge from the hospital.	***Overall study design:*** Prospective study ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** 1 year after discharge ***Reference Score:*** None	***Target population:*** ICU survivors ***# of participants:*** 3655	**Mean *Age:*** 60.1 years (SD=15.0) ***Gender/Sex:*** Not reported
Khoudri et al., 2007	***Country:*** Morocco ***Site:*** Medical ICU of Rabat University Hospital	Arabic version of Short Form-36 (SF-36)	Evaluate the measurement properties of the Arabic version of the short form (SF)-36 and study the HRQL determinants in adult patients 3 months after discharge from an ICU.	***Overall study design***: Prospective study ***Sampling method***: Convenience sampling ***Timing of Assessment:*** 3-month after discharge ***Reference Score:*** None	***Target population:*** ICU survivors ***# of participants:*** 145	**Mean *Age:*** 38.2 years (SD=17) ***Gender/Sex:*** 79 (54%) males
Khoudri et al., 2012	***Country:*** Morocco ***Site:*** Medical ICU of Rabat University Hospital	Arabic version of the EuroQol 5 Dimensions (EQ-5D)	Evaluate the HRQL of a Moroccan cohort' patients alive 3 months after ICU discharge and to assess the psychometric	***Overall study design***: Prospective study ***Sampling method***: Convenience sampling ***Timing of Assessment:*** 3-	***Target population:*** ICU survivors ***# of participants:*** 145	**Mean *Age:*** 38.2 years (SD=17) ***Gender/Sex:*** 79 (54%) males

			properties of the Arabic version for Morocco of the EQ-5D.	month after discharge ***Reference Score:*** SF-36		
Heyland et.al., 2000	***Country:*** Canada ***Site:*** Mixed ICU (Kingston General Hospital)	Short Form-36 (SF-36)	Describe the long-term health-related quality of life (HRQL) of survivors of sepsis and to evaluate the reliability and validity of the medical outcomes study Short Form-36 (SF-36) in this population.	***Overall study design:*** Cross-sectional survey ***Sampling method***: Voluntary response sampling ***Timing of Assessment:*** 16.6 months (SD=10.6) after hospital discharge. ***Reference Score:*** PQOL	***Target population:*** Sepsis survivors (admitted with sepsis or developed sepsis in the ICU) ***# of participants:*** 30	**Mean *Age:*** 62 years (SD=13.7) ***Gender/Sex:*** 14 (46.7%) females
Patrick et al., 1988	***Country:*** United States ***Site:*** Medicine or the Respiratory ICUs	Perceived Quality of Life Scale (PQOL)	Development of a subjective measure of need satisfaction, the Perceived Quality of Life Scale (PQOL).	***Overall study design:*** Not reported ***Sampling method:*** Convenience sampling (who lived within one hour's driving time of the hospital/60 miles) ***Timing of Assessment*:** Interviewed a median of 19 months after discharge ***Reference Score:*** SIP, PGWB	***Target population:*** ICU survivors ***# of participants:*** 77	**Mean *Age:*** 69 years (SD=8) ***Gender/Sex:*** 52% male
Kaarlola et al., 2004	***Country:*** Finland ***Site:*** Medical surgical ICU	EuroQol 5 Dimensions (EQ-5D) and RAND 36-Item Health Survey (RAND-36)	Compare two health-related quality of life measures, EQ-5D with RAND-36 in previous critically ill patients.	***Overall study design:*** Prospective observational Study ***Sampling method:*** Consecutive sampling ***Timing of Assessment*:** Not Reported ***Reference Score:*** None	***Target population:*** ICU survivors ***# of participants:*** 1,099	***Median Age:*** 54 years (range 41-65***)*** ***Gender/Sex:*** 66% male
Tools for Cognitive Impairment Assessment						
Wassenaar et.al 2018	***Country:*** Netherlands ***Site:*** Medical-surgical ICUs (two university hospitals)	CFQ-14 (14 item Cognitive Failures Questionnaire)	Develop and validate an abbreviated version of the Cognitive Failure Questionnaire that can be used by	***Overall study design:*** Retrospective multicenter observational study ***Sampling method:*** Convenience	***Target population***: ICU survivors ***# of participants:*** 1,737 (819 from	***Mean Age:*** Cohort A:62 years (SD=14) Cohort B: 58 years (SD=16) ***Gender/Sex:*** Cohort A: 69% male Cohort B: 62% male

			patients as part of self-assessment to measure functional cognitive outcome in ICU survivors.	sampling (all consecutive adults admitted to the mixed medical-surgical ICUs) ***Timing of Assessment:***12–24 months after ICU discharge ***Reference Score:*** CFQ-25	hospital A, 918 from hospital B)	
Pfoh et.al 2015	***Country:*** United States ***Site***: ICU	Mini-Mental State Examination (MMSE) 26-item Version	Assess whether the MMSE can detect cognitive impairment in survivors of acute respiratory failure.	***Overall study design:*** Cross-sectional secondary analysis ***Sampling method:*** Not reported ***Timing of Assessment:*** 3, 6 and 12 months (3 and 12 months for the ABC trial and 6 and 12 months for the ALTOS study) ***Reference Score:*** Neuropsychological test battery	***Target population:*** ICU survivors ***# of participants:*** 242	***Mean Age***: A*LTOS study:* 49 years (SD not reported) *ABC trial*: 58 years (SD=16) ***Gender/Sex:*** A*LTOS study:* 50% male *ABC trial:* 62% male
Brown et.al, 2018	***Country***: United States ***Site***: ICU	Montreal Cognitive Assessment (MoCA)	Compare the MoCA with neuropsychological tests in a prospective cohort of sepsis survivors.	***Overall study design:*** Prospective pilot study ***Sampling method:*** Not reported ***Timing of Assessment:*** 3 and 6 months after discharge ***Reference Score:*** Neuropsychological test battery	***Target population:*** Sepsis survivors ***# of participants:*** 30	***Mean Age***: Not reported ***Gender/Sex:*** 57% female

Christie et.al, 2006	***Country:*** United States ***Site:*** LDS Hospital	Telephone battery Comprised of: NCSE: Orientation and Judgement; WMS III: digital span, letter number, logical memory, similarities, and controlled oral word association; Hayling sentence completion test	Develop a test battery composed of established instruments to detect cognitive abnormalities in ARDS survivors via telephone interview.	***Overall study design:*** Cross-sectional study ***Sampling method:*** Convenience Sampling ***Timing of Assessment:*** Not reported ***Reference Score:*** In-person telephone battery	***Target population:*** ARDS survivors ***# of participants:*** Derivation population from ARDS Support Center: 79 Validation population from LDS Hospital: 34	***Mean age:*** *Derivation population*: 43 years (SD=12.7) *Validation population*: 49 years (SD=15) ***Gender/Sex:*** *Derivation population*: 85% female *Validation population,* 50% female
Baumbach et al., 2016	***Country:*** Germany ***Site:*** Surgical and mixed ICUs (Jena University Hospital)	German version of FACT-Cog (FACT-Cog adapted)	Measure perceived cognitive impairments in daily life in survivors of critical illness and their family member controls.	***Overall study design:*** Retrospective cohort study ***Sampling method:*** Convenience sampling (all consecutive adults discharged from the mixed and surgical ICUs) ***Timing of Assessment:*** 3 and 6 months after ICU discharge ***Reference Score***: IQCODE	***Target population:*** ICU survivors and family members ***# of participants:*** *3 months:* 127 patients and 52 family members *6 months:* 103 patients and 36 family members	***Median Age:*** Patients: 65 years (range 18-85) Family members: 56.5 years (range 18-85) ***Gender/Sex:*** Patients: 42 females and 85 males Family members: 42 females, and 10 males
Tools for Physical Impairment Assessment						
Chan et al., 2015	***Country:*** United States and Australia ***Site:*** *ALTOS:* 12 hospitals across 5 study sites *ICAP:* 4 academic teaching hospitals *Denehy et al.:* ICU, hospital, and community settings	6-Min Walk Distance (6MWD)	Examine construct validity and responsiveness and estimate minimal important difference (MID) for the 6MWD in patients surviving ARF/ARDS.	***Overall study design:*** Secondary data analysis ***Sampling method:*** Not reported ***Timing of Assessment:*** *ALTOS:* 6 and 12 months follow ups *ICAP and Denehy et al. studies:* 3, 6, and 12 month follow ups *Elliott et al.:* 3 and 6 months after hospital discharge	***Target population:*** Survivors of acute respiratory failure and acute respiratory distress syndrome ***# of participants:*** *ICAP:* 162 *ALTOS:* 183 *Elliott et al.:* 180 *Denehy et al.:* 126	***Mean Age:*** *ICAP*: 48 years *ALTOS*: 48 years *Elliott et al.*: 57 years *Denehy et al*.: 59 years ***Gender/Sex:*** *ICAP*: 93 (57%) males *ALTOS*: 90 (48%) males *Elliott et al*.: 109 (61%) males *Denehy et al*.: 76 (60%) males

	Elliott et al.: 12 hospitals across 3 study sites			***Reference Score:*** SF-36, EQ-5D, HADS, IES-R		
Da Silveira et al., 2018	***Country:*** Brazil ***Site:*** Surgical and non-surgical ICU (Public tertiary hospital)	Barthel Index Katz Index	Assess the functional status of post-ICU patients using the Barthel Index (BI) and the Katz Index (KI) and to assess which is more suitable for this population.	***Overall study design:*** Retrospective longitudinal study ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** 1 month before hospitalization (pre-ICU) -within 48 hours after ICU discharge (Assessment of the BI and KI before hospital admission was made retrospectively) ***Reference Score:*** None	***Target population:*** ICU survivors who were treated with invasive mechanical ventilation (IMV) for at least 24 hours ***# of participants:*** 249	***Median Age:*** 52 years (range 36-61) ***Gender/Sex:*** 133 (53%) males
Corner et al., 2014	***Country:*** United Kingdom ***Site:*** 11-bed intensive care unit in Central London (mixed medical-surgical)	Chelsea Critical Care Physical Assessment tool (CPAx)	Evaluate the construct validity of the Chelsea Critical Care Physical Assessment tool (CPAx) by analyzing the association between CPAx scores and hospital-discharge location, as a measure of functional outcome.	***Overall study design:*** Not reported ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** Scores taken within 24 hours of stepdown from ICU or death ***Reference Score:*** None	***Target population***: ICU survivors ***# of participants:*** 499	***Mean Age***: 62.3 years (SD=18.3) ***Gender/Sex***: Not reported
Corner et al., 2012	***Country:*** United Kingdom ***Site:*** General and trauma CCU (two London teaching hospitals)	Chelsea Critical Care Physical Assessment tool (CPAx)	Develop a scoring system to measure physical morbidity in critical care – the Chelsea Critical Care Physical Assessment Tool (CPAx).	***Overall study design:*** Prospective cohort study ***Sampling method:*** Purposive sampling ***Timing of Assessment:*** On admission, discharge and every Monday,	***Target population:*** Trauma and general critical care patients ***# of participants:*** 33	***Median Age***: 67 years (range 51-75) ***Gender/Sex:*** Male:female ratio 25:8

				Wednesday, and Friday for the duration of CCU stay ***Reference Score:*** SF-36, SOFA, Peak cough flow, AusTOMs, MRC, GCS, Bloomsbury sedation scale		
Schandl, 2014	***Country:*** Sweden ***Site:*** 13-bed general ICU	The predictive screening instrument (Name not given)	Develop a method for early in-ICU prediction of the patient's individual risk for new-onset physical disability two months after ICU stay.	***Overall study design:*** Prospective cohort ***Sampling method:*** Purposive sampling ***Timing of Assessment:*** 2 weeks prior to hospitalization and 2 months post-discharge ***Reference Score:*** KI index, ADL index	***Target population:*** ICU survivors ***# of participants:*** 148	***Mean Age:*** *Physical disability group:* 59 years (SD=17) *Control group:* 51 years (SD=17) ***Gender/Sex:*** *Physical disability group:* 59% male *Control group:* 64% male
Wintermann et al., 2018	***Country:*** Germany ***Site:*** Bavaria Clinic Kreischa - rehabilitation hospital	Multidimensional Fatigue Inventory (MFI-20)	Examine reliability and validity of the MFI-20 in chronically critically ill (CCI) patients after prolonged intensive care treatment.	***Overall study design:*** Prospective cohort ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** 1, 3 and 6 months following the transfer to post-acute ICU ***Reference Score:*** EQ-5D-3L, SCID-I	***Target population:*** ICU survivors ***# of participants:*** 1 month: 195 3 months: 113 6 months: 91	***Median Age:*** 3 months: 61.1 years (range 55.7-65.6) ***Gender/Sex:*** 3 months: 82 (72.6%) males; 31 (27.4%) females
Milton et al., 2019	***Country:*** Sweden, Denmark, and the Netherlands ***Site:*** 10 general ICUs (medical/surgical)	ICU discharge screening tool for prediction of new-onset physical disability (The screening method)	Examine the potential predictors for poor physical outcome and develop a method for prediction of new-onset physical disability 3 months post-ICU.	***Overall study design:*** Multinational prospective observational cohort study ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** 3 months post-discharge	***Target population***: ICU survivors ***# of participants:*** 404	***Median age:*** 65 years (Range not reported) ***Gender/Sex:*** 61% male

				Reference Score: RAND-36, BI, CPAx		
Tools for Mental Health Impairment and PTSD assessment						
Sukantarat et al., 2007	***Country:*** United Kingdom ***Site:*** General ICU	Depression Anxiety and Stress Scale (DASS)	Examine the performance of Depression Anxiety and Stress Scale (DASS) in an ICU survivor population.	***Overall study design:*** Not reported ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** 3 months and 9 months post-discharge ***Reference Score:*** HADS	***Target population:*** ICU survivors ***# of participants:*** 3 months: 51 9 months: 45	***Mean Age:*** 57.4 years (SD=13.6) ***Gender/Sex:*** 29 females; 22 males
Jutte et al., 2015	***Country:*** United States ***Site:*** 13 ICUs at 4 hospitals in Baltimore, Maryland	Hospital Anxiety and Depression scale (HADS)	Conduct a psychometric evaluation of the Hospital Anxiety and Depression Scale (HADS) and to evaluate associations of 2 measures of psychological distress with the HADS Anxiety (HADS-A) and HADS Depression (HADS-D) subscales in acute lung injury (ALI) survivors.	***Overall study design:*** Prospective cohort study ***Sampling method:*** Consecutive sampling ***Timing of Assessment:*** 3 months post-discharge ***Reference Score:*** EQ-5D-3L, SF-36	***Target population:*** ICU survivors, specifically those of acute lung injury (ALI) ***# of participants***: 151	***Median Age:*** 49 years *(*range 40-57) ***Gender/Sex:*** 58% male
Milton et al., 2017	***Country:*** Sweden ***Site:*** Mixed surgical–medical general ICU, Karolinska University Hospital Solna	Post-Traumatic Stress Symptoms Checklist-10 (PTSS-10) Hospital Anxiety and Depression Scale (HADS)	Evaluate whether early screening with validated questionnaires after ICU discharge can identify patients at risk for symptoms of post-traumatic stress, anxiety and depression 3 months after ICU stay.	***Overall study design:*** Prospective observational cohort study ***Sampling method:*** Consecutive sampling ***Timing of Assessment:*** 1 week after discharge and 3 months after discharge ***Reference Score:*** None	***Target population:*** ICU survivors ***# of participants:*** 1 week after discharge: 132 3 months after discharge: 82	***Median Age:*** 62 years (range 41-70) ***Gender/Sex:*** 55 (42%) females

Milton et al., 2018	***Country:*** Sweden, Denmark, and the Netherlands ***Site:*** 10 general ICUs	The psychological risk prediction instrument for use at ICU discharge. (Name not given)	Develop an instrument for use at ICU discharge for prediction of psychological problems in ICU survivors.	***Overall study design:*** Multinational prospective study cohort ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** 3 months post-discharge ***Reference Score:*** HADS, PTSS-14, RAND-36, PHQ-2	***Target population:*** ICU survivors ***# of participants:*** 404	***Median Age:*** 65 years (range 53-73) ***Gender/Sex:*** 61% male
Schandl et al., 2013	***Country:*** Sweden ***Site:*** Mixed adult medical and surgical 13-bed ICU **(**At Karolinska University Hospital, a tertiary care hospital)	Predictive screening instrument (Name not given)	Develop a predictive screening instrument, for use at ICU discharge, to identify patients at risk for post-traumatic stress, anxiety, or depression.	***Overall study design:*** Prospective cohort study ***Sampling method:*** Consecutive sampling ***Timing of Assessment:*** 2 months post-discharge ***Reference Score:*** PTSS-10 HADS, CCI	***Target population:*** ICU survivors ***# of participants:*** 150	***Mean Age:*** *With adverse psychological outcomes:* 54 years (range 38-65) *Without adverse psychological outcomes:* 60 years (range 45-68) ***Gender/Sex:*** *With adverse psychological outcomes:* 46% female *Without adverse psychological outcomes:* 37% female
Karanikola, et al., 2020	***Country:*** Cyprus ***Site:*** Mixed ICUs	Cypriot version of DTS-I-M (CDTS-I-T)	Translate English version of DTS-I-M to Cypriot version and explore the feasibility, reliability, and validity of the Cypriot version DTS-I-M for use in Greek-speaking ICU survivors in Cyprus.	***Overall study design:*** Cross-sectional descriptive correlational study ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** 2 to 12 months after discharge ***Reference Score:*** DTS-I-M English version	***Target population:*** ICU survivors; comprehension of Greek language ***# of participants:*** 69	***Mean Age:*** 57.81 years (SD=11.78) ***Gender/Sex*** 68.1% male
Scragg et al., 2000	***Country:*** United Kingdom ***Site:*** General ICU (Chelsea and Westminster Hospital)	Experience after Treatment in Intensive Care 7 Item Scale (ETIC-7)	Describe a new measure of psychological distress specifically related to the experience of intensive care management, the	***Overall study design:*** postal questionnaire study ***Sampling method:*** Convenience sampling	***Target population:*** ICU survivors ***# of participants:*** 80 participants	***Median Age:*** 57.1 years (range 19-90) ***Gender/ Sex:*** 38 females; 42 males

			Experience after Treatment in Intensive Care 7 Item Scale and compare it to the other scales.	***Timing of Assessment***: Not reported ***Reference Score:*** TSC-33, IES, HADS		
Hosey et al., 2019	***Country:*** United States ***Site:*** 40+ hospitals across the USA, and 13 ICUs at four hospitals in Baltimore, Maryland	Impact of Event Scale-6 (IES-6)	Evaluate the internal consistency, criterion validity, and external construct validity of the IES-6 in ARDS survivors.	***Overall study design:*** Secondary analysis of two prospective studies ***Sampling method:*** Secondary sampling ***Timing of Assessment:*** 3 months-5 years ***Reference Score:*** IES-R, CAPS, SF-36, HADS, EQ-5D	***Target population:*** ARDS/ICU survivors ***# of participants:*** 1001 participants	***Mean Age:*** 49 years (SD=14) ***Gender/Sex:*** 51% female
Warlan et al., 2016	***Country:*** United States ***Site:*** Medical and surgical ICU (Tertiary level academic medical center in San Diego, California)	Post-Traumatic Stress Syndrome 14 (PTSS-14)	Examine the feasibility and acceptability of Post-Traumatic Stress Syndrome 14 (PTSS-14) to detect posttraumatic stress syndrome after intensive care.	***Overall study design:*** Single-center cross-sectional design ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** 2 to 4 weeks after discharge ***Reference Score:*** PTSD Diagnostic scale experience questionnaire	***Target population:*** ICU survivors ***# of participants:*** 41 participants	***Mean Age:*** 49 years (SD=16.3) ***Gender/Sex:*** 28 males; 13 females
Bienvenu et al., 2013	***Country:*** United States ***Site:*** ARDSNet clinical centers across the United States, and 13 ICUs at four hospitals in Baltimore, Maryland	Impact of Event Scale-Revised (IES-R)	Evaluate the Impact of Events Scale-Revised (IES-R), a questionnaire measure of PTSD symptoms, against the Clinician-Administered PTSD Scale (CAPS).	***Overall study design:*** Secondary analysis of two prospective cohort studies (ALTOS and ICAP) ***Sampling method:*** Secondary sampling ***Timing of Assessment:*** 1 to 5 years after acute lung injury (ALI) ***Reference Score:*** CAPS	***Target population:*** ALI survivors ***# of participants:*** 77 in total *ALTOS:* 47 patients *ICAP:* 30 patients	***Mean Age:*** *ALTOS:* 49 years (SD=12) *ICAP:* 54 years (SD=13) ***Gender/Sex:*** *ALTOS:* 33% male *ICAP:* 44% male
Parsons et al., 2018	***Country:*** United States	Sleep item on the PTSD Checklist – Civilian version	Examine the validity of a single item from the	***Overall study design:*** Secondary	***Target population:***	***Mean Age:*** 48.1 years (SD=13.5) ***Gender/Sex:***

	Site: Medical-surgical ICU (Harborview Medical Center)	(PCL-C sleep item)	PTSD checklist-Civilian version (PCL-C) to detect insomnia by Insomnia Severity Index (ISI).	analysis of data from a longitudinal study ***Sampling method:*** Secondary sampling ***Timing of Assessment***: 12 months after discharge ***Reference Score:*** ISI, PHQ-9, SF-12	Medical-surgical ICU survivors ***# of participants:*** 120	57.5% male
Nickel et al., 2004	***Country:*** Germany ***Site:*** Gastroenterological and pulmonological-internal medicine ICUs (Erlangen University)	Posttraumatic Scale (PTSS-10)	Examine reliability of the PTSS-10 (PTSD customarily diagnosed as 35 points or higher) in the diagnostic context of the Structured Clinical Interview (SCID I and II) for the DSM-IV.	***Overall study design:*** Cross-sectional study ***Sampling method***: Simple random sampling ***Timing of Assessment:*** 3 to 15 months after discharge ***Reference Score:*** SCID	***Target population:*** ICU survivors ***# of participants:*** 41	***Mean Age:*** 47.2 years (SD not reported) ***Gender/Sex:*** 28 (68.3%) male
Jubran et al., 2010	***Country:*** United States ***Site:*** Long-term acute care hospital (RML Specialty Hospital)	Post-traumatic stress syndrome questionnaire (PTSS-10)	Determine whether the PTSS-10 questionnaire could be used as a screening test for subsequent development of PTSD after weaning from prolonged mechanical ventilation.	***Overall study design:*** Single center prospective longitudinal study ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** 1 week after weaning and 3 months after weaning ***Reference Score:*** SCID	***Target population***: ICU survivors who received mechanical ventilation and had been weaned from the ventilator ***# of participants:*** 41	***Mean Age:*** 66 years (range 59-72) ***Gender/Sex:*** 15 females; 26 males
Stoll et al., 1999	***Country:*** Germany ***Site:*** Multidisciplinary ICU (Ludwig-Maximillians University teaching hospital)	Post-traumatic stress syndrome questionnaire (PTSS-10)	Modify and validate an existing PTSS-10 questionnaire for diagnosis of PTSD in a cohort of Long-term survivors of acute respiratory distress syndrome (ARDS).	***Overall study design:*** Follow-up cohort study ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** >6 months after ICU discharge, two assessments two years apart ***Reference Score***: SCID	***Target population:*** Long-term survivors of ARDS ***# of participants:*** 52	***Median Age:*** 36.5 years (range 18-50) ***Gender/Sex:*** 26 males, 26 females

Twigg et al., 2008	***Country:*** United Kingdom ***Site:*** Two ICUs in two UK general hospitals	UK Post-traumatic stress syndrome 14-questions inventory (UK-PTSS-14)	Conduct a preliminary validation of the UK- Post-Traumatic Stress Syndrome 14-Questions Inventory (UK-PTSS-14).	***Overall study design:*** Case series cohort study ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** 4-14 days, 2 months, and 3 months after discharge ***Reference Score:*** PDS, IES	***Target population***: ICU survivors ***# of participants:*** 44	***Median Age***: 56 years (range 18-74 at Hospital A, and 25-63 at Hospital B) ***Gender/Sex:*** Hospital A: 21 females, 18 males Hospital B: 3 females, 2 males
Rosendahl et., 2019	***Country:*** Germany ***Site:*** ICUs in 5 study centers in Germany (acute care hospital setting in Jena, Halle/Saale, Leipzig, Bad Berka, Erfurt)	Post-traumatic stress syndrome (PTSS-10) questionnaire, Post-traumatic stress syndrome (PTSS-14) questionnaire (German version), Posttraumatic Stress Disorder Checklist (PCL-5)	Compare the validity of three screening instruments (PTSS-10, PTSS-14, PCL-5) to assess symptoms of posttraumatic stress disorder (PTSD) after intensive care of sepsis.	***Overall study design:*** Smaller observational study within a multicenter patient cohort study ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** Approximately 4 months after intensive care of sepsis/septic shock ***Reference Score:*** CAPS-5	***Target population:*** Adult ICU survivors, particularly of sepsis or septic shock ***# of participants:*** 83	***Median Age:*** 64 years (range 56-71) ***Gender/Sex:*** 60.02% male
Tools for PICS-Family Assessment						
Kentish-Barnes et al., 2016	***Country:*** France ***Site:*** 41 French ICUs	CAESAR	Develop and validate a tool specifically designed to assess the overall experience of relatives of patients who die in the ICU.	***Overall study design:*** Mixed methods study for tool development and multicenter prospective study for validation ***Sampling method:*** Convenience sampling ***Timing of Assessment:*** 21 days after the death ***Reference Score:*** HADS, IES-R	***Target population:*** Relatives of patients who died in the ICU ***# of participants:*** Main sample relatives: 430 Validation sample relatives: 116	***Mean Age***: Not reported ***Gender/Sex:*** For a sample of 413, 31% male; 69% female

We were unable to draw conclusions regarding the overall quality of studies due to inadequate information (Table 2). In all studies, the stability of the instrument was measured in

clinically relevant time intervals. However, the duration between repeated administrations in some tools was small, which is suggestive of a 'priming effect' (Table 1). Our analysis revealed inadequate blinding among raters which could have resulted in bias. An important consideration is that most studies employed convenience sampling which may have possibly resulted in samples not being adequately representative of the post-ICU population, as patients with either highest or lowest severity of post-ICU symptoms might have been more difficult to reach or have declined participation. Moreover, confounding factors (i.e., related to sampling technique, time of administration, comorbidities) were not controlled in most cases. Additionally, the appropriateness of the statistical method for analysis and study interpretation employed was of concern for few studies (Table 2).

Table 2: Appraisal of identified studies using the Quality Appraisal of Diagnostic Reliability (QAREL) Checklist

Article	**Item 1 Was the test evaluated in a sample of subjects who were representative of those to whom the authors intended to be applied?**	**Item 2 Was the test performed by raters?**	**Item 3 Were raters blinded to the findings of other raters?**	**Item 4 Were raters blinded to their own prior findings?**	**Item 5 Were raters blinded to the results?**	**Item 6 Were raters blinded to the clinical information?**	**Item 7 Were raters blinded to additional clues not part of the test?**	**Item 8 Was the order of the examination varied?**	**Item 9 Was the stability of the variable being measured considered when determining the suitability of the time interval among repeated measures?**	**Item 10 Was the test applied correctly?**	**Item 11 Were appropriate statistical measures of agreement used?**	**Sufficient evidence of reliability**
Tools for PICS Assessment												
Akerman et al., 2009	Yes	No	NA	NA	Unclear	NA	Unclear	NA	Yes	Yes	No	Unclear
Akerman et al., 2012	Yes	No	NA	NA	Unclear	NA	Unclear	NA	Yes	Yes	Yes	Unclear
Malmgren et al., 2021	Yes	No	NA	NA	NA	NA	Unclear	NA	Yes	Yes	Yes	Unclear

Wang et al., 2019	Yes	Yes	Unclear	Unclear	Unclear	No	Unclear	NA	No	Yes	Yes	Unclear
Spies et al., 2019	Yes	Yes	Unclear	NA	Unclear	Unclear	Unclear	NA	Unclear	Yes	No	Unclear
Jeong et al., 2019	Yes	No	NA	NA	NA	NA	Unclear	NA	No	Yes	Yes	Unclear
Kang et al., 2020	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Yes	Yes	Yes	Unclear
Bergbom, et al., 2018	Yes	No	NA	NA	NA	NA	Unclear	NA	Yes	Yes	Yes	Unclear
Chrispin, 1996	Yes	No	NA	NA	NA	NA	Unclear	NA	NA	Yes	Yes	Unclear
Tian and Miranda, 1994	Yes	Yes	Unclear	NA	Unclear	Unclear	Unclear	NA	NA	Yes	No	Unclear
Khoudri et al., 2007	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Yes	Yes	Unclear
Khoudri et al., 2012	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Yes	Yes	Unclear
Heyland et al., 2000	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	NA	NA	Yes	Yes	Unclear
Patrick et al., 1988	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	NA	NA	Yes	Yes	Unclear
Kaarlola et al., 2004	Yes	No	NA	NA	NA	NA	Unclear	NA	Yes	Yes	Yes	Unclear
Tools for Cognitive Impairment Assessment												
Wassenaar et.al 2018	Yes	No	NA	NA	NA	NA	Unclear	NA	Unclear	Yes	Yes	Unclear
Pfoh et al., 2015	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Yes	Yes	Yes	Unclear
Brown et al., 2018	Yes	Yes	NA	Unclear	Unclear	Unclear	Unclear	NA	Yes	Yes	No	Unclear
Christie et al., 2006	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	No	Unclear
Baumbach et al., 2016	Yes	No	NA	Unclear	Unclear	Unclear	Unclear	NA	Yes	Yes	Yes	Unclear
Tools for Physical Impairment Assessment												
Chan et al., 2015	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Yes	Yes	Yes	Unclear

Da Silveira et al., 2018	Yes	Yes	NA	Unclear	Unclear	Unclear	Unclear	NA	Yes	Yes	Yes	Unclear
Corner et al., 2014	Yes	Yes	Unclear	NA	NA	Unclear	Unclear	NA	Yes	Yes	No	Unclear
Corner et al., 2012	Yes	Yes	Yes	Yes	NA	Unclear	Unclear	NA	Yes	Yes	Yes	Unclear
Schandl et al., 2014	Yes	Yes	Unclear	NA	NA	Unclear	Unclear	NA	Yes	Yes	No	Unclear
Wintermann et al., 2018	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Yes	Yes	Yes	Unclear
Milton et al., 2019	Yes	No	NA	NA	NA	NA	Unclear	NA	Yes	Yes	Yes	Unclear
Tools for Mental Health Impairment and PTSD Assessment												
Sukantarat et al., 2007	Yes	No	NA	NA	Unclear	NA	Unclear	NA	Yes	Yes	Yes	Unclear
Jutte et al., 2015	Yes	Yes	Unclear	NA	Unclear	Unclear	Unclear	NA	Yes	Yes	Yes	Unclear
Milton et al., 2017	Yes	No	NA	NA	NA	NA	Unclear	NA	Yes	Yes	Yes	Unclear
Milton et al., 2018	Yes	No	NA	NA	NA	NA	Unclear	NA	Yes	Yes	No	Unclear
Schandl et al., 2013	Yes	No	NA	NA	NA	NA	Unclear	NA	Yes	Yes	Yes	Unclear
Karanikola, et al., 2020	Yes	Yes	Unclear	NA	Unclear	Unclear	Unclear	NA	Yes	Yes	Yes	Unclear
Scragg et al., 2000	Yes	No	NA	NA	NA	NA	Unclear	NA	Yes	Yes	Yes	Unclear
Hosey et al., 2019	Yes	No	NA	NA	NA	NA	Unclear	NA	Yes	Yes	Yes	Unclear
Warlan et al., 2016	Yes	Unclear	Unclear	NA	NA	Unclear	Unclear	NA	NA	Yes	Yes	Unclear
Bienvenu et al., 2013	Yes	Yes	Unclear	Unclear	No	Unclear	Unclear	NA	Unclear	Yes	Yes	Unclear
Parsons, et al., 2018	Yes	Unclear	Unclear	NA	Unclear	Unclear	Unclear	NA	Yes	Yes	Yes	Unclear
Nickel et al., 2004	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	NA	Yes	Yes	Yes	Unclear

Jubran et al., 2010	Yes	No	NA	NA	Yes	NA	Yes	NA	Yes	Yes	Yes	Yes
Stoll et al., 1999	Yes	No	NA	NA	Unclear	Yes	Unclear	NA	No	Yes	Yes	Unclear
Twigg 2008	Yes	Yes	Unclear	No	No	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear
Rosendahl et al., 2019	Yes	No	NA	NA	NA	NA	Unclear	NA	Yes	Yes	Yes	Yes
Tools for PICS-Family Assessment												
Kentish-Barnes et al., 2016	Yes	No	NA	NA	NA	NA	Unclear	NA	Yes	Yes	Yes	Unclear

In a few studies, patients were engaged in the process of instrument development and/or validation, either through patients' interviews or direct patient involvement (Bergbom et al., 2018; Corner et al., 2012; Malmgren et al., 2021; Spies et al., 2019; Jeong et al., 2019; Karanikola et al., 2020; Kentish-Barnes et al., 2016). However, the population involved in instrument development in most cases was small and stable. Instead, it is more likely that the sicker patients might not be involved in the development of the identified instruments. Also, there is no evidence that tool administrators, such as health professionals and research assistants, received standard training for tool administration in some of the studies (Da Silveira et al., 2018; Corner et al., 2012; Heyland et.al., 2000; Jutte et al., 2015; Karanikola et al., 2020; Khoudri et al., 2012; Khoudri et al., 2007; Nickel et al., 2004; Parsons et al., 2018; Patrick et al., 1988; Schandl et al., 2013; Schandl 2014; Twigg et al., 2008; Wang et al., 2019; Warlan et al., 2016). Most importantly, there was an unequal representation of sex/gender across studies, with overrepresentation of male participants. In contrast, there was a notable overrepresentation of female participants in studies that included family caregivers. Therefore, more study is needed to assure validity of instruments in both sexes and genders.

The tools presented were either self-administered, administered by research staff, or healthcare professional (trained nursing staff, psychometrists, or physiotherapists). Most of the tools were sent via mail and participants completed them with no assistance (Akerman et al., 2009; Akerman et al., 2012; Baumbach et al., 2016; Bergbom et al., 2018; Chrispin 1996; Hosey et al., 2019; Jiyeon et al., 2020; Jubran et al., 2010; Kaarlola et al., 2004; Malmgren et al., 2021; Milton et al., 2019; Milton et al., 2017; Milton et al., 2018; Rosendahl et al., 2019; Schandl et al., 2013; Scragg, et al., 2000; Sukantarat et al., 2007; Stoll, et al., 1999; Tian and Miranda, 1994; Warlan et al., 2016; Wassenaar et al., 2018). Only a few tools were administered through interview (i.e., in-person or via telephone by the research staff or health care professionals) (Christie et al, 2006; Corner et al., 2012; Corner et al., 2014; Heyland et.al., 2000; Khoudri et al., 2007; Khoudri et al., 2012; Patrick et al., 1988; Pfoh et.al, 2015; Wang et al., 2019**)**. Most studies used patient-reported measures but did not report on how tools were administered (Table 3).

Feasibility was addressed in a handful of studies (Karanikola et al., 2020; Schandl et al., 2013; Spies et al., 2019; Warlan et al., 2016). In most cases, the time required to complete the questionnaires was not reported (Akerman et al., 2009; Akerman et al., 2012; Baumbach et al., 2016; Bergbom et al., 2018; Bienvenu et al., 2013; Brown et.al., 2018; Chan et al., 2015; Corner et al., 2012; Corner et al., 2014; Da Silveira et al., 2018; Heyland et.al., 2000; Hosey et al., 2019; Jubran et al., 2010; Jutte et al., 2015; Kaarlola et al., 2004; Karanikola et al., 2020; Khoudri et al., 2007; Khoudri et al., 2012; Malmgren et al., 2021; Milton et al., 2017; Milton et al., 2018; Milton et al., 2019; Nickel, et al., 2004; Parsons et al., 2018; Patrick et al., 1988; Pfoh et.al 2015; Rosendahl et al., 2019; Schandl et al., 2013; Schandl et al., 2014; Scragg et al., 2000; Stoll et al., 1999; Sukantarat et al., 2007; Tian and Miranda, 1994; Twigg et al., 2008; Warlan et al., 2016; Wassenaar et al., 2018; Wintermann et al., 2018). However, from the available data it can be

concluded that the shorter the instrument, the less time patients needed to complete them. For instance, the PICSQ included 18 items and took less than five minutes to complete (Kang et al., 2020) and the HABC-M SR, which consist of 27 items to assess PICS, took approximately five minutes to complete. Contrastingly, the OMI set, which is the combination of four different tools, took 20 minutes for the initial screening and 85-110 minutes for the extended assessment by health care professionals (Spies et al., 2019). Similarly, completion of the CAESAR tool required 20 minutes for family caregivers of patients who died in the ICU to complete (Kentish-Barnes et al., 2016). Moreover, there is evidence that use of shorter instruments resulted in higher response rate, increased completion, efficiency, and higher data quality. CFQ-14 when compared to CFQ-25 was perceived as less burdensome to survivors resulting in increased response rates and efficiency (Wassenaar et al., 2018). Similarly, IES-6 when compared with the original IES-R, demonstrated improved efficiency, while maintaining adequate measurement properties in screening for PTSD symptoms.

Table 3: Description of identified tools

Author & Date	**Name and Focus of Tool**	**Tool Development**	**Components of Tool and Measurement**	**Tool Administration**	**Comparison with Gold standard**	**Psychometric and diagnostic properties**
Akerman et al., 2009	3-Set 4P Questionnaire PICS: Physical and psychosocial problems	Questionnaire was developed from a literature review and from clinical and theoretical experiences of ICU nurses regarding health and recovery after ICU. The primary tool consists of 53 items: 16 physical	Made up of three sets and 43 items: • **Physical sets** (four factors and 11 items): 1. Body change a. Physical health b. Skin c. Swallowing d. Muscles 2. Change in appearance a. Appearance b. Lost hair c. Weight 3. Physical condition a. Physical condition b. Mobility	Self-reported Questionnaires sent by mail	12-Item Short Form Health Survey (SF-12)	***Reliability:*** ***Internal consistency***: Cronbach's alpha (α) (0.70-0.85) • Physical set: 0.703 • Psychosocial set: 0.848 • Follow-up set: 0.823 ***Stability reliability***: • For the set of physical problems, r_s>0.5 in 8 of 11 items. • For the set of psychosocial problems, r_s>0.5 in 19 of 22 items. • For the set of follow-up ICU care, r_s>0.5 in 2 of 10 items

		items, 26 psychosocial items and 11 follow-up ICU care items.	4. Nutrition a. Appetite b. Diarré • **Psychosocial set** (five factors and 22 items): 1. Sleep and mood a. Wellbeing b. Fall a sleep c. Nightmares d. Back to sleep e. Anxiety f. Tearful g. Irritation h. Depressed 2. Memory a. Memory b. Name c. Daily d. Concentration 3. Hallucination a. Hallucination b. Discuss c. Problem 4. Avoid a. Event memory b. Avoidance c. Avoid places d. Alone 5. Social life a. Social life b. Harmony c. Relation • **Follow-up set** (four factors and 10 items): 1. Help to understand a. Work problem b. Help c. Speak 2. Filling the memory gap a. Understanding b. Memory gap c. Conversation 3. Meaning with ICU follow-up a. Follow-up b. Help/support 4. Information a. Need to speak b. Information Items measured through a 5-point Likert scale based			***Validity:*** ***Construct validity***: • Physical problem: Total variance 72.9% and factor loadings 0.6-0.8 • Psychosocial problem: Total variance 70.9% and factor loadings 0.51-0.86 • Follow-up ICU care: Variance 86.6% and factor loadings 0.43 and 0.96 ***Concurrent validity***: Good overall correlation compared to the SF 12 (r_s> 0.5) ***Sensitivity:*** Not reported ***Specificity:*** Not reported

			on participant's level of agreement from ''strongly agree'' to ''do not agree at all''			
Akerman et al., 2012	3-Set 4P questionnaire PICS: Physical and psychosocial problems	The questionnaire was previously developed and tested for validity and reliability in a pilot study. The previous questionnaire was modified according to recommendations and was then further developed and tested.	Consists of three sections: Physical, psychosocial and follow-up. Included closed-ended questions. • **''Physical problems'' set included 10 questions and 3 factors:** 1. Physical limitations (4 questions), 2. Change in appearance (4 questions) 3. Physical condition (2 questions) • **''Psychosocial problems'' set included 19 questions and 5 factors:** 1. Memory (5 questions), 2. Mood (6 questions), 3. Social life (3 questions), 4. Avoidance (2 questions) 5. Sleep (3 questions) • **''Follow-up'' set included 14 questions and 4 factors:** 1. Information (5 questions) 2. Help in recovery (4 questions), 3. Realizing the critical illness (3 questions) 4. Help with problems (2 questions) Likert scale measuring level of agreement with four to five responses from ''Strongly Agree'' to ''Do not agree at all''. One response option was ''Not Relevant''.	Self-reported Questionnaire sent by mail	36-Item Short Form Health Survey (SF-36)	***Reliability:*** ***Internal consistency***: Overall Cronbach's α score > 0.70. • Physical problems: α=0.75 • Psychosocial problems: α =0.84 • Follow-up: α =0.91 ***Stability reliability:*** • The ICC for the Physical set (10 questions): three poor, three fair, three moderate and one strong • The ICC for the Psychosocial set (19 questions): one poor, seven fair and 11 moderate. • The ICC for the Follow-up set (14 questions), six strong, seven moderate and one fair ***Validity:*** ***Concurrent validity:*** Correlations between 3-Set 4P and the SF-36 were significant for all 11 questions • Spearman's r_s moderate in eight questions and weak in five questions ***Construct validity:*** • 3 factor Physical set: Variance 64.2% • 5 factors Psychosocial set: Variance 62.6% • 4 factors Follow-up set: Variance 77.5% ***Sensitivity:*** Not reported ***Specificity:*** Not reported

Malmgren et al., 2021	Provisional questionnaire for long-term health-related quality of life and burden of disease after intensive care PICS: Physical, cognitive, and mental health	Followed recommendations of EORTC (European Organization of Research and Treatment of Cancer) and the Division of Clinical Cancer Epidemiology, Gothenburg, Sweden to develop the questionnaire. Created a comprehensive list of symptoms and issues using data saturation, and parallel process of data collection and analyses. Interviews were taken by interviewers with clinical experience and domain knowledge. Single interview of ICU survivors at least six months after discharge. Semi-structured technique to explore current situation, symptoms, difficulties, quality-of-life issues, and social effects arising at any point after ICU discharge.	**13 domains and 238 questions:** 1. Cognition (31) 2. Fatigue (14) 3. Physical health (31) 4. Pain (19) 5. Psychological health (29) 6. Activities of daily living (16) 7. Sleep (11) 8. Appetite and Alcohol (11) 9. Sexual Health (14) 10. Sensory Functions (26) 11. Gastrointestinal Functions (7) 12. Urinary Functions (8) 13. Work Life (21) **Of the 238 questions**, • 113 questions on a 6-point scale • 91 questions on a 5-point scale • Eight questions on a 4-point scale • Two questions on a 3-point scale • 22 questions were measured on a dichotomous scale • Two questions were quantitative	Self-reported Sent to participants	Not reported	***Reliability:*** Not reported ***Validity:*** ***Content validity:*** • Questionnaire based mainly on issues reported by ICU survivors • All interviewees were read the field notes to ensure our proper understanding of issues. • All questions were tested with cognitive interviews on additional ICU survivors ***Sensitivity:*** Not reported ***Specificity:*** Not reported

		Domains and issues from previous interviews, literature or other scales and questionnaires were used as probes.				
Wang et al., 2019	Healthy Aging Brain Care-Monitor Self Report (HABC-M SR) PICS: Physical, cognitive, and mental health	Validated already developed tool in ICU survivors	**27 items and three subscales:** 1. Cognitive (six questions about memory, orientation, and judgment) 2. Functional (11 questions about activities of daily living) 3. Psychological (10 questions about depression, psychotic, and anxiety symptoms) Rated on the patient's perceived frequency of the symptom over the past two weeks: 0 = Not at all (0–1 day), 1 = several days (2–6 days), 2 = More than half of the days (7–11 days), 3 = Almost daily (12–14 days)	Self-reported, administered in-person by a healthcare professional or psychometrist Takes as little as five minutes	1. **For cognition:** Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB) 2. **For psychological symptoms:** Geriatric Depression Scale-30 (GDS-30), Patient Health Questionnaire-9 (PHQ-9), Post-Traumatic Symptom Scale (PTSS-10)	***Reliability:*** • Overall internal consistency: Cronbach's α =0.83-0.92 • The inter-scale correlation between all the subscales: α =0.61–0.70 ***Validity:*** ***Construct validity:*** • The psychological subscale had the strongest correlations with PHQ-9 (Spearman correlation coefficient 0.73), GDS-30 (Spearman correlation coefficient 0.74), and PTSS-10 (Spearman correlation coefficient 0.68). • The cognitive subscale strongly correlated with only the delayed memory measure of the CERAD-NB (Spearman correlation coefficient −0.51) and no correlation with any of the measures on the RBANS. • The functional subscale correlated with the PSMS (Spearman correlation coefficient −0.26). ***Sensitivity:*** Not reported ***Specificity:*** Not reported

					3. **For physical functioning:** Physical Self-Maintenance Scale (PSMS)	
Spies et al., 2019	OMI set PICS: Physical, cognitive, and mental health	Based on recent evidence on outcomes in ICU survivors, a preliminary OMI set was chosen and discussed in the consensus meetings. Predefined selection criteria were: (1) Free-of-charge, non-commercial application; (2) Time for completion of the set not exceeding 20–30 min in total; (3) Potentially administrable by a variety of clinical practitioners; (4) Validated measurement properties in clinical patient populations, including adults of all age groups; (5) Existence of a validated German version. 14 participants from nine stakeholder groups participated in the first and second consensus	**OMI set used in two-step process** **Step 1 PICS Screening:** 1. Mental health: • Patient Health Questionnaire-4 (PHQ-4)) 2. Cognition: • MiniCog, Animal Naming 3. Physical function: • Timed Up-and-Go (TUG) • Handgrip strength **4.** Health-related quality of life: • EQ-5D-5L **Step 2 PICS Extended assessment:** 1. Mental health: • Patient Health Questionnaire-8 (PHQ-8) • Generalized Anxiety Disorder Scale-7 (GAD-7) • Impact of Event Scale – revised (IES-R) 2. Cognition: • Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) • Trail Making Test (TMT) 3. Physical function: • 2-Minute Walk Test (2-MWT) • Handgrip strength • Short Physical Performance Battery (SPPB) **4.** Health-related quality of life:	**Step 1 PICS Screening OMI set**: Self-reported and administered by a healthcare professional after a short instruction**.** This step took 20 minutes to complete. **Step 2 PICS Extended assessment OMI set:** Self-reported and administered by a healthcare professional familiar with PICS patients. This step took 85 to 110 minutes to complete.	Not reported	***Reliability:*** Not reported ***Validity:*** Not reported ***Sensitivity:*** Not reported ***Specificity:*** Not reported

		meeting. Final OMI set was made by a core group of six clinical researchers.	• EQ-5D-5L • 12-Item WHO Disability Assessment Schedule (WHODAS 2.0)			
Jeong et al., 2019	Post-Intensive Care Syndrome Questionnaire (PICSQ) PICS: Physical, cognitive, and mental health	Generated through relevant literature reviews, qualitative interviews among survivors, and multiple rounds of content validity evaluations by experts	PICSQ included three factors and 18 items: 1. Mental (6 items) 2. Cognitive (6 items) 3. Physical (6 items) Four-point Likert scale: 0 (Never), 1 (Sometimes), 2 (Most often), or 3 (Always)	Self-reported How tools were administered or distributed was not reported < 5 minutes to complete	Japan Frailty Scale (JFS) SF-36	***Reliability:*** • Overall internal consistency: Cronbach's α = 0.93. • Internal consistency of each 'subfactor': α for the mental subfactor = 0.87; for the cognitive subfactor = 0.90, and physical subfactor = 0.84 • Test-retest reliability for each factor between the first and second measures were r = 0.82-0.88 ($p < .001$) and the correlation between the two total scores was r = 0.90 ($p < .001$) ***Validity:*** ***Construct validity:*** • The variance of the PICSQ items selected through exploratory factor analysis = 64.0% ***Convergent validity:*** • Standardized factor loading>0.50 ***Discriminant validity***: • Met the criteria that the value of ''r ± 2 × standard deviation" between factors should not include 1 ***Criterion validity:*** • The correlation between PICSQ and JFS was r=0.73 ($p < .001$). • The correlation between PICSQ and SF-36 was r = -0.38 ($p < .001$) for PCS and r = -0.51 ($p < .001$) for MCS ***Sensitivity:*** Not reported ***Specificity:*** Not reported
Kang et al., 2020	Post-Intensive Care Syndrome Questionnaire (PICSQ)	Relevant nurses and physicians evaluated the tool in the present study	PICSQ included three factors and 18 items: 1. Mental (6 items) 2. Cognitive (6 items) 3. Physical (6 items)	Self-reported Distributed to participants	Not reported	***Reliability:*** • Overall internal consistency: Cronbach's α = 0.92 ***Validity:*** Not reported

	PICS: Physical, cognitive, and mental health		Rated using 4-point Likert scale (0 = never, 4 = always)	Approximately 5 minutes to complete		***Sensitivity:*** • Based on the optimal cut-off values determined by the authors (23.00 for the raw score and 23.73 for weighted score, with AUCs of .933 and .929, respectively***)*** = 85.5% ***Specificity:*** • ***At*** 23.00 and 23.73 points=80.9 and81.5% respectively
Bergbom et al., 2018	Recovery After INtensive Care (RAIN) PICS: Physical, cognitive, and mental health	30 items were constructed by the authors based on: 1. Previous research on patients' recovery following ICU care 2. Patient interviews 3. Thoughts and ideas about integration, health, and recovery Further evaluated and analyzed by independent expert group consisting of four faculty members and pilot tested on eight ICU survivors which resulted in 36 questions for this tool	**20 items and six factors**: 1. Forward looking (4 items) 2. Supporting relations (4 items) 3. Existential ruminations (4 items) 4. Revaluation of life (3 items) 5. Physical and mental strength (3 items) 6. Need of social support (2 items) The tool placed an emphasis on spiritual and existential thoughts as a focus. 5-point Likert scale ranging from 1-No/Never to 5-Yes/ Very Much/Often.	Self-reported Sent via mail	Not reported	***Reliability:*** ***Internal item consistency:*** • Cronbach's α for all scales ranged from 0.75-0.90 ***Validity:*** ***Content validity index (CVI)*** was acceptable ***Construct validity:*** • 75% variance • Eigen value>1 ***Convergent validity*** • item-scale correlations > 0.40 (mean value range=0.57-0.78) ***Discriminant validity:*** • Item-scale discriminant validity was satisfactory ***Sensitivity:*** Not reported ***Specificity:*** Not reported
Chrispin, 1996	36-Item Short Form (SF-36) Health-related Quality of life	Used already developed SF-36 to examine whether it could be answered by patients at discharge from the ICU and to	Eight dimensions and 36 questions: 1. Physical Functioning (10) 2. Role Physical (4) 3. Bodily Pain (2) 4. General Health (5) 5. Vitality (4) 6. Social Functioning (2) 7. Role Emotional (3)	Self-reported and administered by trained nursing staff. The questionnaire took 15-20	Not reported	***Reliability:*** ***Internal consistency***: • Cronbach's α >0.85 for all components (except mental health 0.77) • Correlation coefficient among items: 1. Physical Functioning: 0.55-0.81

		measure the reliability and validity of their replies.	8. Mental Health (5)	minutes to complete.		2. Role Physical: 0.84-0.91 3. Bodily Pain: 0.95 4. General Health: 0.12-0.77 5. Vitality: 0.74-0.82 6. Social Functioning: 0.77 7. Role Emotional: 0.71-0.85 8. Mental Health: 0.57-0.72 ***Reliability coefficient:*** >0.75 ***Validity:*** ***Construct validity:*** • Significant difference in the distribution of scores due to age (F =6:29, p < 0:01), sex (F =9:20, p < 0:01) and interaction between age and sex (F =5:20, p < 0:01) ***Content validity*** was good as suggested by wide range of scores in six out of the eight dimensions ***Sensitivity:*** Not reported ***Specificity:*** Not reported
Tian and Miranda, 1994	Sickness Impact Profile (SIP) Health-related Quality of life	Not reported	12 categories and 136 questions: 1. Ambulation (number of questions) 2. Mobility 3. Body Care 4. Social Interactions 5. Alertness Behavior 6. Emotional Behavior 7. Communication 8. Sleep and Rest 9. Eating 10. Work 11. Home Management 12. Recreation and Pastimes Each of the 136 questions is an objective statement with scale values and can be answered as: Yes/No/Does not apply.	Self-reported and self-administered Mailed to the patients	Not reported	***Reliability:*** Not reported ***Validity:*** • Factor-loadings >0.46 • Factor analysis has shown that the SIP structure in patients after intensive care is like that described in the original paper ***Sensitivity:*** Not reported ***Specificity:*** Not reported

Khoudri et al., 2007	Arabic version of Short Form-36 (SF-36) Health-related Quality of life	Used the already validated Arabic version of the SF-36 in ICU survivors	Eight dimensions and 36 questions: 1. Physical Functioning (10) 2. Role Physical (4) 3. Bodily Pain (2) 4. General Health (5) 5. Vitality (4) 6. Social Functioning (2) 7. Role Emotional (3) 8. Mental Health (5)	Self-reported 84 (58%) participants were interviewed in consultation and 61 (42%) participants were interviewed by telephone by the same interviewer	Not reported	***Reliability:*** ***Internal consistency*** • α >0.70 ***Test–retest reliability****:* • Intraclass correlation coefficient >0.40 ***Validity:*** • Multitrait scaling analysis confirmed discriminant validity • Known-groups comparison to test for hypothesized differences about gender, age, and comorbidity confirmed construct validity ***Sensitivity:*** Not reported ***Specificity:*** Not reported
Khoudri et al., 2012	Arabic version of the EuroQol 5 Dimensions (EQ-5D) Health-related Quality of life	Translated the United Arab Emirates Arabic version using EuroQol group guidelines and input by an experienced consultant who is a native speaker of Moroccan Arabic and fluent in English "Usual activities" was changed to "Daily activities". Prayer" was added to the Leisure dimension. "Walking" was added to the Mobility dimension. "Discomfort" was changed to "Not to Feel	Two Sections: **First Section**: "self-classifier" covers five dimensions: Mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Resposes ranged from "No problems", "Moderate problems", or "Extreme problems". **Second Section**: Visual analogue scale comprised of a 20 cm 'thermometer', with 100 representing 'best imaginable health state' and 0 representing worst imaginable health state.	Self-reported 84 (58%) were interviewed in consultation and 61 (42%) were Interviewed by telephone and by the same interviewer	SF-36	***Reliability:*** ***Intraclass correlation coefficient:*** • EQ-VAS = 0.92 • EQ-5D index = 0.95 ***Kappa statistic (EQ-5D self-classifier):*** • Mobility = 0.73 • Self-care = 0.49 • Usual activities = 0.66 • Pain/discomfort = 0.92 • Anxiety/depression = 0.72 ***Validity:*** ***Criterion validity:*** • Spearman correlation coefficients between EQ-5D index and SF-36 ranged between 0.53-0.79. • Pearson correlation coefficients between EQ-VAS and SF-36 ranged between 0.42-0.62. ***Construct validity*** of the EQ-5D was confirmed since differences in EQ-5D index and EQ-VAS scores were found between groups of patients ***Sensitivity:*** Not reported

		Good Physically" to account the socio-cultural context and Moroccan day-life. Tested on five respondents irrelevant to healthcare professions and the report was sent to the EuroQol Group business management to finalize the Arabic version of the EQ-5D for Morocco.				***Specificity:*** Not reported
Heyland et al., 2000	Short Form-36 (SF-36) Health-related Quality of life	Validated already developed SF-36 in sepsis survivors	Eight dimensions and 36 questions: 9. Physical Functioning (10) 10. Role Physical (4) 11. Bodily Pain (2) 12. General Health (5) 13. Vitality (4) 14. Social Functioning (2) 15. Role Emotional (3) 16. Mental Health (5)	Self-reported via telephone administration	Patrick's Perceived Quality of Life Scale (PQOL)	***Reliability:*** ***Test-Retest Reliability****:* Intraclass correlation coefficient >=0.75 for both summary scales ICC for SF-36 domain: • Physical functioning = 0.56 • Role physical = 0.88 • Bodily pain = 0.81 • General health = 0.58 • Vitality = 0.58 • Social functioning = 0.56 • Role emotional = 0.96 • Mental health = 0.86 ***Internal Consistency Reliability****:* • Cronbach's α >0.70 for both summary scales and for seven of the eight domains of the SF-36 ***Validity:*** ***Construct validity:*** • Significant correlations between the MCS and PQOL scores and the PCS and PQOL scores. Pearson correlation coefficient

						• 0.56 and 0.45 respectively. ***Sensitivity:*** Not reported ***Specificity:*** Not reported
Patrick et al., 1988	Patrick's Perceived Quality of Life Scale (PQOL) Health-related Quality of life	The PQOL scale was developed based upon circumscribed areas that encompass those fundamental needs that define the quality of an individual's life: physical, psychological, social, activity, material, and structural.	11 items describing fundamental needs of daily living: 1. The health of your body (HEALTH) 2. Your ability to think and remember (THINKING) 3. How happy you are (HAPPINESS) 4. How much you see your family and friends (FAMILY) 5. The help you get from family and friends (HELP) 6. Your contribution to the community (COMMUNITY) 7. Your activities outside work (LEISURE) 8. How your income meets your needs (INCOME) 9. How respected you are by others (RESPECT) 10. The meaning and purpose of your life (MEANING) 11. With working/not working/retirement (WORK) Participants rated their level of satisfaction on a scale from 0 to 100 (higher scores indicate greater satisfaction)	Self-reported via in-person interview	Sickness Impact Profile (SIP) Psychological General Well-Being Schedule (PGWB)	***Reliability:*** ***Internal consistency:*** • $\alpha = 0.88$ ***Validity:*** ***Construct validity:*** • Low to moderate correlation between perceived life quality and other health status domains. • PQOL was more closely related to affective status (PGWB) than to behavioral dysfunction (SIP). ***Sensitivity:*** Not reported ***Specificity:*** Not reported
Kaarlola et al., 2004	EQ-5D and RAND Health-related Quality of life	Compared validated Finnish versions of the EQ-5D and the RAND-36 questionnaires.	**EQ-5D:** Five dimensions measured using a 20-cm vertical visual analogue scale (EQ-VAS) and rated from "0" (worst imaginable health state) to "100" (best imaginable health state). The dimensions included mobility, self-care, usual	Self-reported Mailed to the survivors	Not reported	***Reliability:*** Not reported ***Validity:*** ***Construct validity:*** • Individual and summary elements of the EQ-5D and the RAND-36 correlated strongly. • Respondents with low EQ-sum indices tended to have very low scores on Physical and Emotional

			activities, anxiety/depression, and bodily pain. Each dimension has three possible options: 1 = no problem 2 = moderate problem 3 = severe problem **RAND** Eight domains: 1. Physical Functioning 2. physical Role Limitations 3. Emotional Role Limitations 4. Vitality 5. Mental Health 6. Social Functioning 7. Painlessness 8. General Health			Role Limitation of the RAND-36. • Discriminatory power of the EQ-5D was weaker, especially with Mobility, Self-Care, and lower QOL values due to the ceiling effect. ***Sensitivity:*** Not reported ***Specificity:*** Not reported
Wassenaar et al., 2018	14-item Cognitive Questionnaire (CFQ-14) Cognitive impairment	Abbreviated version of the CFQ-25 Used a linear regression model to select out the optimal subset of CFQ items. Criteria to determine the optimal model for the abbreviated CFQ were a minimal number of CFQ items with the maximum R2 possible and proportional coverage of the items on the dimensions: memory, distractibility, social blunders, and names.	**Four Components:** 1. Memory (4 questions) 2. Distractibility (5 questions) 3. Social blunders (4 questions) 4. Names (1 question) **Measurement:** Five-point Likert scale ranging from "Never" (0) to "Very Often" (4)	Self-reported	25-item Cognitive Failure Questionnaire (CFQ-25)	***Reliability:*** • Pearson's correlation between CFQ-14 and the CFQ-25 =0.986 ***Validity:*** • Bland-Altman plot shows agreement among CSQ-25 and CSQ-14 • Variance=>98% compared with the original 25-item CFQ ***Sensitivity:*** Not reported ***Specificity:*** Not reported

Pfoh et al 2015	MMSE 26-item Version Cognitive impairment	Used already developed 26 item MMSE (Telephone version)	**5 cognitive domains**: 1. **Orientation** to time and place 2. **Registration** of three words 3. **Attention**: backward spelling of 'WORLD' 4. **Memory**: recall of three words 5. **Language**: naming, repetition and following a three-stage command	Administered via telephone/ in person by research assistants who underwent detailed training,	Neuropsychological test battery	**ALTOS (**at 6 and 12 months) ***Inter-rater Reliability (Kappa score*):** 0.19 and 0.34 ***Overall agreement***: 67% and 80% ***AUROC curve***: 0.66 and 0.76 ***Sensitivity:*** 24%, 30% ***Specificity:*** 93%, 97% ***Positive predictive value:*** 67% and 76% ***Negative predictive values:*** 67% and 81% **ABC trial (**at discharge, 3 months, and 12 months) ***Inter-rater Reliability, Kappa score***: 0.09, 0.10 and 0.12 ***Overall agreement***: 42%, 38% and 42% ***Sensitivity*** =37%, 22% and 19% ***Specificity***: 100% ***Positive predictive value***: 100% ***Negative predictive values***: 13%, 25% and 33%
Brown et al. 2018	MoCA Cognitive impairment	Used already developed MoCA	Not reported	In-person by trained research coordinators	Neuropsychological test battery	**For threshold 25** ***Inter-rater reliability*****,** • **Concordance correlation coefficient (CCC)**: 0.34 • **K score**: 0.37 and 0.32 for 3 and 6 months ***Validity*** • Cognitive domain scores of neuropsychological testing and MoCA were moderately correlated, r=0.34-0.62. ***Sensitivity***: 92% and 71% for 3 and 6 months ***Specificit:*** =47% and 62% for 3 and 6 months **For threshold 24** ***Inter-rater reliability*****,** ***CCC***: 0.41 ***Sensitivity***: 77% and 59%

						Specificity: 71% and 77%
Christie et al, 2006	Telephone battery Cognitive impairment	Battery of tests derived from standardized assessment tools, created with the help of interdisciplinary team of researchers including specialists in rehabilitation medicine, psychometrics, brain injury, ARDS, and neuropsychology	**6 domains**: 1. Orientation 2. Attention 3. Working memory (concentration) 4. Memory 5. Reasoning (Abstract and practical) 6. Executive functions	Telephone interview by 1 of 2 research personnel, both trained in cognitive test administration 20 to 30 minutes	Comparing between In-person and telephone	***Reliability:*** ***Interclass Reliability*** *(Pearson correlation)* • WMS-III (Digital span) =0.37 • Controlled oral word association=0.60 • WAIS-III (similarities)=0.61 • WMS-III (Logical memory I) = 0.45 ***Validity:*** ***Construct validity in the Derivation Population*** **Convergence:** • Significant association between cognitive impairment detected by the telephone battery and Mental Health Summary Score of the SF-36, P=0.08 • Significant association between cognitive impairment detected by the telephone battery and SIP psychosocial summary, P=>0.001 **Divergent:** • No association between cognitive impairment detected by the telephone battery and SF-36 Physical Summary Score, P=0.3646 • No association between Cognitive impairment detected by the telephone battery and SIP physical summary score, P= 0.25 ***Convergent validity in the external validation population*** • Telephone tests showed good correlation with in-face interviews (except for the Hayling Sentence Completion Test and the WMS-III Letter-Number Sequencing Test) ***Sensitivity:*** Not reported

						Specificity: Not reported
Baumbach et al., 2016	German version of FACT-Cog (FACT-Cog $_{adapted}$) Cognitive impairment	Adapted version of the English FACT-Cog (FACT-Cog $_{adapted}$) Steps: 2 independent translators provided a first German version of the items. A revised German version was composed based on the judgments of one trained neuropsychologist and one trained psychologist. Final questionnaire composed through back translation and comparison with the original version with the help of a trained linguist.	**Questionnaire comprises 4 subscales and 37 items** 1. Perceived Cognitive Impairments (PCI, 20 items) 2. Comments from Others (CFO, 4 items) 3. Perceived Cognitive Abilities (PCA,9 items) 4. Interference with Quality of Life (IQL, 4 items) **Measurement:** **For PCI and CFO items**, 5-point Likert scale (0 "never", 4 = "several times a day"). **PCA and IQL items,** 5-point Likert scale (0 = "not at all", 4 = "very much").	Self-reporting Contacted via mail	Informant questionnaire on cognitive decline in elderly (IQCODE)	***Reliability:*** Cronbach's α, ○ PCI=0.954 ○ CFO=0.763 ○ PCA=0.941 ○ IQL=0.944 ***Validity:*** • Spearman rank correlation coefficients between the subscales and IQCODE scores: PCI=0.269 CFO=0.125 PCA=0.186 IQL=0.169 • Item-convergent validity, PCI=100% CFO=100% PCA=1000% IQL=100% • Item-discriminant validity, PCI=95% CFO=100% PCA=1000% IQL=100% ***Sensitivity:*** Not reported ***Specificity:*** Not reported
Chan et al., 2015	6-Min Walk Distance (6MWD) Functional status	Used already developed 6MWD	**Elements of this tool included:** - 4-m timed walking speed - Manual muscle testing - Spirometry	Patient-reported but unclear about how tool was administered.	36-item short form (SF-36): *PF domain and MH domain* Euro-QOL (EQ-5D): *Mobility and Anxiety Domain* HADS *Anxiety symptoms*	***Reliability:*** Not reported ***Validity:*** ***Convergent validity***: • physical health outcomes strongly correlated (r>0.40) with 6MWD ***Discriminant validity***: • weak relationships (r<0.30) between mental health outcomes and 6MWD ***Predictive validity***: • 3-5% (future mortality, rehospitalization, alive-at-home status, return to

					IES-R *PTSD Symptoms*	normal activity, and HRQL) ***Responsiveness:*** • Positive SF-36 PF domain changes between 3 and 6 months were associated with 6MWD increases of 65 (95% CI, 46-83) m compared with 26 (95% CI, 9-42) m for the no-change group and 29 (95% CI, 53 to 5) m for the negative change group ***Minimal important difference (MID***)= 20-30m ***Sensitivity:*** Not reported ***Specificity:*** Not reported
Da Silveira et al., 2018	Barthel Index Katz Index Functional status	Applied already developed tools	**Barthel Index** **- 10 ADLs** -Feeding, bathing self, personal hygiene, dressing, bowel control, bladder control, toilet, chair/bed transfer, ambulation, stair climbing -scored based on level of assistance required by patient the lower the value, the more dependent the patient **Katz Index** **-6 ADLs** -bathing, dressing, toileting, transferring, continence, and feeding - Utilizes a 3-point Likert scale (1- need for non-human assistance, 2-need for human assistance, 3-complete dependence)	Self-reported Interviewed by a single researcher	Compared BI and KI	***Reliability:*** ***relative variation,*** • BI: 0.44 (0.11–0.67) • KI: 0.55 (0.30–0.80) ***Validity:*** fair correspondence between the original scores and the scores calculated by the IRT analysis • ***correlation (pre-ICU scores)*** = 0.59 and -0.73 for the BI and KI, respectively. • ***correlation (post-ICU scores)*** = 0.95 and -0.94 for the BI and KI, respectively.
Corner et al., 2014	Chelsea Critical Care Physical Assessment tool (CPAx) functional status	Used already developed CPAx tool	Tool measures 10 components of physical function: 1. respiratory function, 2. cough, 3. bed mobility, 4. supine to sitting on the edge of the bed,	Administered by trained ICU physiotherapists Average of 2 minutes to complete	Not reported	***Reliability:*** Good interrater reliability in previous studies, according to authors ***Validity:*** Evidence of good construct validity

			5. dynamic sitting, 6. sit to stand, 7. standing balance, 8. transferring from bed to chair, 9. stepping, and 10. grip strength graded on a 6-point Guttman Scale, from complete dependence to independence (0 to 5)			0.8% ceiling effect and a 3.2% floor effect ***Sensitivity:*** Not reported ***Specificity:*** Not reported
Corner et al., 2012	Chelsea Critical Care Physical Assessment tool (CPAx) functional status	Developed by using classic test theory through an iterative process including content validity questionnaires, an expert focus group, service-user feedback, and an extensive pilot study on a cohort of 33 ICU patients.	**10 components** of physical function: 1. respiratory function, 2. cough, 3. bed mobility, 4. supine to sitting on the edge of the bed, 5. dynamic sitting, 6. sit to stand, 7. standing balance, 8. transferring from bed to chair, 9. stepping, and 10. grip strength graded on a 6-point Guttman Scale, from complete dependence to independence (0 to 5)	Administered by physiotherapists	*SF-36* SOFA Peak cough flow AusTOMs MRC GCS Bloomsbury sedation scale	***Reliability:*** ***Internal consistency***, Cronbach's α = 0.798 ***Inter-rater reliability***, κ = 0.988 (95% confidence interval 0.791 to 1.000) ***Validity:*** ***Content validity*** indices CVI of 1.00 (P < 0.05). ***Construct validity****:* Spearman's rank correlation coefficient between CPAx and: • Peak cough flow, r=0.633 • MRC, r= 0.650 • SOFA, r=−0.683 • GCS, r= 0.764 • Bloomsbury sedation scale, r=0.420 • SF-36 (physical component) and pre-admission CPAx score, r= 0.720 • SF-36 (physical component) and discharge CPAx score, r= 0.843 • mental component of the SF-36, *r* = 0.024 • AusTOMs MSK score (activity), r=0.735 • AusTOMs MSK score impairment, r=0.763 • AusTOMs BPC score (activity), r= 0.903 • AusTOMs BPC score (impairment), r= 0.874 ***Sensitivity:*** Not reported ***Specificity:*** Not reported

Schandl, 2014	The predictive screening instrument functional status	23 potential predictors were selected through a literature review and clinician feedback (e.g., ICU physicians, nurses, physiotherapist, occupational therapists, psychologists). Finally, the potential predictors and adverse outcome were evaluated through logistic regression model.	**4 predictors:** 1. low educational level 2. impaired core stability 3. fractures 4. ICU stay >2 days. Total risk calculated based on the presence of each risk factor at ICU discharge. For presence of every risk predetermined score is added. Predetermined Scores: 1. Education level elementary school= 57 2. Reduced core stability=45 3. Fractures= 45 4. ICU length of stay > 2 days=30	Assessed by clinicians	2 Different ADL scales were used to assess functional status - Pre- ICU: Katz ADL index - Post- ICU: ADL staircase	***Reliability:*** interrater agreement was above 0.9 ***Validity:*** Fair predictive validity AUC= 0.82 and the 1,000 bootstrap cross validated AUC was 0.80 (95% CI 0.69 to 0.90) ***Sensitivity:*** Not explicitly reported ***Specificity:*** Not explicitly reported
Wintermann et al., 2018	Multidimensional Fatigue Inventory (MFI-20) functional status	Used already developed tool	**5 sub-scales with 20-item to** measure of fatigue **5 sub-scales:** 1. general fatigue (GF) 2. physical fatigue (PF) 3. mental fatigue (MF) 4. reduced motivation (RM) 5. reduced activity (RA) 5-point Likert scale (range 1- "yes, that is true" to 5- "no, that is not true")	self-report Telephone interview trained study nurse	-Euro-Quality of Life (EQ-5D-3 L) -Structured Clinical Interview for the Diagnostic and Statistical Manual of mental disorders DSM-IV (SCID-I)	***Reliability:*** ***Internal consistency***, • Cronbach's α = .91 • Pearson item subscale correlation coefficient ranged from 0.11 to 0.58 ***Validity:*** • composite reliability (CR) was appropriate (CR > .7) for all MFI subscales at both ***time points.*** • Significant correlation between the MFI-total and EQ-5D-3 L at both 3 months and 6 months (range: - 65 to -66). • Significant correlations between the MFI-total and SCID-I (range: .27–.37) • Floor effects, 26.5% had the lowest possible test score at 3 months, and 20.9% at 6 months ***Sensitivity:*** Not reported ***Specificity:*** Not reported
Milton et al.,2019	ICU discharge screening tool for prediction of new-	16 potential predictors were selected using a	**5 elements** 1. supine to sitting on the edge of the bed	Self-reported	RAND-36 (physical component)	***Reliability:*** ***Interrater reliability***

	onset physical disability (The screening method) functional status	literature search and "expert consensus discussion". Further, associations between risk factors and the primary outcome were investigated with univariable logistic regression analysis. Physical status at ICU discharge was the only predictor associated after multivariable analysis with backward elimination.	2. cough 3. moving within the bed 4. dynamic sitting, 5. respiratory function	delivered to participants through mail	BI CPAx	• moderate for cough, supine to sitting and moving within the bed, • substantial for dynamic sitting, • almost perfect for respiratory function ***Validity:*** AUC=0.68 (95% CI 0.67-0.68). ***Sensitivity:*** 73% ***Specificity:*** 60% ***Positive predictive value*** =0.32 (95% CI 0.25-0.40) ***Negative predictive value*** =0.88 (95% CI 0.83-0.91),
Sukantara t et al., 2007	Depression, Anxiety, and Stress scale (DASS) psychological impairment	Used already developed tool	**42 questions** in total, 14 for each if **3 subscales**: 1. depression 2. anxiety 3. stress Each question is scored from 0 ('does not apply to me at all') to 3 ('applies to me very much, or most of the time').	Self-report	HADS	***Reliability:*** ***internal consistency*** for each DASS subscale, Cronbach's α = 0.92 – 0.95 ***Validity:*** ***Criterion validity***: • Strong correlation between HADS and DASS for anxiety (r = 0.88), and depression (r = 0.93) ***Sensitivity***: Not reported ***Specificity:*** Not reported
Jutte et al., 2015	Hospital Anxiety and Depression scale (HADS) psychological impairment	Used already developed HADS tool	**14 items from 2 subscales**: 1. Anxiety: i. Tense/Wound up ii. Frightened feeling iii. Worrying thoughts iv. Feel relaxed v. Butterflies in stomach vi. Feel restless	research assistants	EQ-5D-3L SF-36	***Reliability:*** ***Internal consistency***, • HADS-A, Cronbach's α = .79 • HADS-D, Cronbach's α = .70 ***Validity:*** • EQ-5D anxiety/depression item with HADS-A and D, AUROC= 0.74 and 0.66

			vii. Feelings of panic anxiety 2. Depression: i. Still enjoy things ii. Can laugh iii. Feel cheerful iv. Feel slowed down v. Lost interest in appearance vi. Look forward with enjoyment vii. Enjoy book, TV, radio			• SF-36 mental health with HADS-A and D, AUROC= 0.84 and 0.73 • EQ-5D-3L anxiety/depression item was positively correlated with HADS-A and D, r = 0.54 and 0.41 • SF-36 mental health was negatively correlated with and HADS-A and D, r = -0.70 and -0.51 ***Sensitivity:*** • EQ-5D anxiety/depression item with HADS-A and D= ***0.77 and 0.73*** • SF-36 mental health with HADS-A and D=***0.82 and 0.73*** ***Specificity:*** • EQ-5D anxiety/depression item with HADS-A and D=***0.65 and 0.57*** • SF-36 mental health with HADS-A and D=***0.72 and 0.60***
Milton et al., 2017	Post-Traumatic Stress Symptoms Checklist-10 (PTSS-10) Hospital Anxiety and Depression Scale (HADS) psychological impairment (PTSD, anxiety, and depression)	Used already developed tools: PTSS-10 and HADS	**PTSS-10 consists of 2 parts:** 1. **Part A**: 4 questions about memories of trauma in the ICU (nightmares, panic, anxiety) - Questions answered with 'yes' or 'no' 2. **Part B**: 10 questions about current stress symptoms - Items are scored from 1 (never) to 7 (always) **HADS includes 2 subscales with 7 items each.** **1.** Anxiety **2.** Depression - Each subscale is scored from 0 to 3	Self-reported patients returned questionnaires by postal mail	Not reported	***Reliability:*** Not reported ***Validity:*** • PTSS, AUROC= 0.90 • HADS anxiety, AUROC of 0.80 • HADS depressive, AUROC= 0.75 ***Sensitivity:*** • PTSS-10 for scores > 34= 91% • HADS anxiety for score > 7= 77% • HADS depressive for score > 7=76% ***Specificity:*** • PTSS-10 for scores > 34= 86% • HADS anxiety for score > 7= 75% • HADS depressive for score > 7= 66% ***Positive predictive value***: • PTSS-10 =50% • HADS anxiety=37% • HADS depressive=37% ***Negative predictive value*** = • PTSS-10 =98%

						• HADS anxiety=95% • HADS depressive=91%
Milton et al., 2018	The psychological risk prediction instrument for use at ICU discharge psychological impairment	18 potential risk factors from 3 categories (1) premorbid risk factors, (2) in-ICU risk factors and (3) ICU discharge risk factors, were selected after searching the literature and a consensus discussion with a panel of experts. Of the 18 potential risk factors, 4 were included in the final prediction model after multivariable logistic regression analysis	**4 predictors**: 1. age 2. lack of social support 3. traumatic memories (PTSS-14-A) 4. symptoms of depression at ICU discharge (PHQ-2) **Total risk calculated from sum of age, PTSS14-A, PHQ-2, and social support**: • Age score varies from 0-58 and total score calculated according to developed table • Use PTSS14-A to assess traumatic memories scores. Final score is calculated by multiplying total number of yes by 5 • Use 4-point Likert PHQ-2 scale from 0 to 3 points (0=not at all and 3= nearly all the time) to assess symptoms of depression at ICU discharge. Final score is calculated by adding the assessed scores and multiplying by 3. • social support scored BASED ON yes/no response. 16 points added for a NO response.	Self-reported questionnaires sent by postal mail	HADS PTSS-14 RAND-36 PHQ-2	***Reliability:*** Not reported ***Validity:*** • AUC= 0.73 (95% CI 0.73–0.74) in 500 bootstrap samples • Shrinkage factor= 0.89 ***Sensitivity:*** Not reported ***Specificity:*** Not reported ***Positive predictive value*** = 0.83 (95% CI 0.37-0.98) ***Negative predictive value*** = 0.84 (95% CI 0.79-0.88)
Schandl et al., 2013	Predictive screening instrument psychological impairment	Risk factors for psychological morbidity after critical illness and specific factors influencing psychological recovery in general identified through literature review and consensus discussion with ICU clinicians running a follow-	**Six predictors** were included in the final screening instrument: **1.** Major pre-existing disease **2.** parent to children younger than 18 **3.** previous psychological problems, **4.** In-ICU agitation **5.** Unemployed/sick leave at time of ICU admission **6.** appearing depressed in the ICU -First, assess which predictors the patient has at	Self-reported In-person at time of discharge but does not report who administered	PTSS-10 HADS Carlson Comorbidity Index (CCI)	***Reliability:*** Not reported ***Validity:*** ***Predictive validity***, as determined by AUROC curve, was 0.77 (0.72 after cross-validation in 1000 bootstrap samples) ***Sensitivity:*** Not reported ***Specificity:*** Not reported

		up clinic, and a clinical psychologist specialized in traumatic stress. 21 potential risk factors were selected for further analysis based on: a) the applicability for a heterogeneous critically ill population b) the feasibility for ICU clinicians to assess the risk factor c) a fair possibility of assessment before the patient left the ICU.	the time of discharge to the ward. Total risk score is the sum of individual risk scores.			
Karanikola, et al., 2020	Cypriot version of DTS-I-M (CDTS-I-T) PTSD in ICU survivors	DSM IV; Translated from English to Greek. Revision and validation occurred from five experts with experience in critical care, instrumentation, and mental health nursing. Further validation and notes on feasibility provided by two volunteers with ICU hospitalization experiences	**imilar to DTS-I-M (English version), 17 items.** Items may be grouped into: 1. intrusive re-experiencing symptoms, for example, nightmares (items 1-5) 2. avoidance symptoms, for example, avoiding any thoughts or feelings about the event (items 6, 7) 3. cognitive (not being able to recall the event) and emotional/ mood (unable to have sad or loving feelings/difficulty enjoying things) disturbance symptoms (items 8, 9, 10, 11, 12, 14), 4. symptoms of hyperarousal, for example, insomnia	telephone interviews	The English version of DTS-I-M	***Reliability:*** ***internal consistency reliability***, • Cronbach's α =0.945 ***test-retest reliability***, • Pearson's $r = 0.928$, $P < .001$ ***Validity:*** ***construct validity*** • factor analysis confirming a 3-factor PTSD model, variability= 77.75% • Kaiser-Meyer-Olkin (KMO) index value = 0.628 ***Sensitivity:*** Not reported ***Specificity:*** Not reported

			(items 8, 13, 15, 16, 17). 5-point Likert scale for both the frequency (from 0 [never] to 4 [every day]) and the severity (from 0 [no disturbing] to 4 [extremely disturbing]) of symptoms during the preceding 2 weeks, which are then multiplied, and this product reflects a DTS-I-M item score, with a range from 0 to 16. The total DTS-I-M score ranges from 0 to 272 (16 × 17)			
Scragg, et al., 2000	Experience after Treatment in Intensive Care 7 Item Scale (ETIC-7) post-traumatic stress directly related to ICU	Authors identified seven criteria for PTSD using the Diagnostic and Statistical Manual of Mental Disorders 4th edition specifically from the trauma re-experiencing and trauma-stimuli avoiding symptom clusters. Finally, constructed 7 questionnaires items that specifically reflect experience of ICU treatment.	**7 questions:** 1. Have you had upsetting thoughts or images about your time in the Intensive Care Unit that came into your head when you didn't want them to? 2. Have you experienced `flashbacks' which make you feel as if you are back in the Intensive Care Unit? 3. Have you felt upset when you were reminded of your stay in the Intensive Care Unit? 4. Have you had bad dreams or nightmares about your time in the Intensive Care Unit? 5. When reminded of your stay in the Intensive Care Unit, does it make you feel anxious or unwell (for example, heart racing or thumping, nausea, sweating)? 6. Have you tried not to think about, talk about, or have feelings about your time in the Intensive Care Unit? 7. Have you tried to avoid activities, people or places that remind you of the Intensive Care Unit (for	Self-reported Self-administered questionnaire sent by mail	Trauma Symptom Checklist 33 (TSC-33) Impact of Events Scale (IES) Hospital Anxiety and Depression Scale (HADS)	***Reliability:*** ***internal consistency,*** • Cronbach's α = 0.84 ***Validity:*** ***concurrent validity*** • ETIC-7 scores showed stronger correlations with the IES and TSC-33 scores, and HADS anxiety scores than with the HADS depression scores. • Pearson correlation, ECTIC-7 with: o IES total 0.5 o IES intrusions 0.57 o IES avoidance 0.39 o HADS total 0.54 o HADS anxiety 0.61 o HADS depression 0.37 o TSC-33 total 0.56 ***Sensitivity:*** Not reported ***Specificity:*** Not reported

			example, doctors' appointments, visiting hospital or television programs about hospitals)? 4-point Likert scale ranging from not at all (0), rarely (1), sometimes (2), and often (3)			
Hosey, et al., 2019	Impact of Event Scale 6 (IES-6) PTSD in ARDS survivors	Developed by abbreviating the IES-R tool	**6 items** The instrument includes 6 items from the 22-item IES-R 1. item no 6: I thought about it when I did not mean to 2. item no 21: I felt watchful or on-guard 3. item no 3: Other things kept making me think about it 4. item no 12: I was aware that I still had a lot of feelings about it, but I didn't deal with them 5. item no 11: I tried not to think about it 6. item no 18: I had trouble concentrating 5-point Likert scale: "not at all" (0), "a little bit" (1), "moderately" (2), "quite a bit" (3), or "extremely" (4).	Self-reported administered by trained research staff at scheduled follow-up assessments	Impact of Event Scale-Revised (IES-R) Clinician Administered PTSD Scale (CAPS) SF-36 HADS EQ-5D-3L	***Reliability:*** ***internal consistency,*** • correlation of the IES-R and the IES-6 = 0.96 (0.94 to 0.97) • Cronbach's α =0.85 to 0.91 ***Validity:*** ***External construct validity***, Pearson correlations (r) value when compared IES-6 with: • SF-36 Mental Health Domain, r=0.42; 95% CI, 0.39 to 0.46 • Mental Component Summary, r=0.46; 95% CI, 0.42 to 0.49 • HADS Anxiety Subscale, r=0.52; 95% CI, 0.49 to 0.55 • HADS Depression Subscale, r=0.40; 95% CI, 0.37 to 0.44 • EQ-5D-3L Anxiety/Depression Item, r=0.32; 95% CI, 0.28 to 0.35). ***Criterion validity,*** • Comparison of the IES-6 to CAPs, AUROC= 0.93 (95% CI, 0.86 to 1.00) ***Sensitivity:*** 0.88 ***Specificity:*** 0.85 ***Positive predictive value:*** 0.47 ***Negative predictive value:*** 0.98
Warlan, et al., 2016	Post-Traumatic Stress Syndrome 14 (PTSS-14) screening tool	Used already validated PTSS-14 screening tool to examine its	**14-item:** 1. Sleep problem 2. Nightmares 3. Depression 4. Jumpiness	self-reported telephone call interview	PTSD Diagnostic Scale Screening Experience Questionnaire	***Reliability:*** internal consistency, • Cronbach's α = 0.90 ***Validity:*** Not reported

	PTSS in ICU survivors	feasibility and acceptability.	5. The need to withdraw from others 6. Irritability 7. Frequent mood swings 8. guilt feelings 9. Fear of places and situations reminding intensive care unit 10. Muscular tension 11. Upsetting, unwanted thoughts or images of time on the intensive care unit 12. Feeling numb 13. Avoid places, people or situations that remind of the intensive care unit 14. Feeling as if plans or dreams for the future will not come true 7-level Scores range from 14 to 98; the higher the score, the greater the level of PTSS Score of 45 or higher may be related to PTSD			***Sensitivity:*** Not reported ***Specificity:*** not reported ***Feasibility and acceptability,*** Participants response to the PTSS-14 instrument: • "Very easy to understand" = 90% • "Completed in an acceptable period of time" =98% • "Caused little distress" =7% • "Caused no distress" =88%
Bienvenu, et al., 2013	22 item Impact of Event Scale-Revised (IES-R) PTSD in acute lung injury (ALI) survivors	Evaluated already developed IES-R screening tool in ALI survivors	**22 items from 3 subscales**: 1. Intrusion 2. Avoidance 3. Hyperarousal 5-point Likert scale ranging from "not at all" (item score 0), "a little bit" (score, 1), "moderately" (score, 2), "quite a bit" (score, 3), or "extremely" (Score, 4).	Self-reported administered by trained research staff face to face (75%) or via telephone (25%)	Clinician Administered PTSD Scale (CAPS)	***Reliability:*** ***internal consistency,*** • Cronbach's α = 0.96 ***Validity:*** ***discriminant validity***, • area under the ROC curve is 95% (95% CI, 88%-100%) ***concurrent validity,*** • IES-R total scores highly correlated with CAPS total severity scores • Pearson *r*= 5 0.80 • Spearman r =5 0.69 ***Sensitivity:*** 80 to 100% ***Specificity:*** 85 to 91% ***positive predictive value***=50% to 75% ***negative predictive value***= 93% to 100%

Parsons et al., 2018	Sleep item on the PTSD Checklist – Civilian version (PCL-C sleep item) Insomnia among ICU survivors	Used single sleep item from the 17-item PTSD Checklist – Civilian version (PCL-C).	Single sleep item on the PCL-C Rates subjects' difficulty initiating or maintaining sleep over the past month (0 [not at all] to 5 [extremely]).	self-reported telephone	Insomnia Severity Index (ISI) Patient Health Questionnaire-9 (PHQ-9) SF-12	***Reliability:*** Not reported ***Validity:*** ***convergent validity*** • Spearman's rank correlation coefficients between PCL sleep item score and o PHQ-9summary score, ρ = 0.64 o PCL-C summary score, ρ = 0.62 o SF-12 domain scores, ρ = -0.18 to -0.38 ***criterion validity*** • AUC = 0.85 (95% CI: 0.78 – 0.92) • The PCL-C sleep item score correlated significantly with ISI score (Spearman's rank correlation coefficient = 0.75 (P < 0.01). ***Sensitivity:*** • item score≥3= 91% • item score ≥ 4= 67% ***Specificity:*** • item score≥3=67% • item score ≥ 4= 86% ***Positive Predictive Value:*** • item score≥3= 51% • item score ≥ 4= 65% ***Negative Predictive Value:*** • item score≥3= 95% • item score ≥ 4= 87%
Nickel et al., 2004	Posttraumatic Scale (PTSS-10) PTSD among ICU survivors	Compared PTSD diagnosed with PTSS-10 and SCID.	**10 statements** focusing on reactions to traumatic events Rated in 7-point Likert scale ranging from 1 point (never) to 7 points (always) on each statement	Self-reporting Telephone interview	Structured Clinical Interview (SCID)	***Reliability:*** Not reported ***Validity:*** Not reported ***Sensitivity:*** Not reported ***Specificity:*** Not reported Almost twice as many PTSD cases were diagnosed among the subjects with the PTSS-10 compared with SCID o Screening with PTSS-10 showed that 17.07% of the patients met the recommended threshold for probable diagnosis of

						PTSD of 35 or more points. o With SCID, PTSD could be confirmed in 9.76% of the cases.
Jubran et al., 2010	Post-traumatic stress syndrome questionnaire (PTSS-10) PTSD after weaning from prolonged mechanical ventilation	Used validated PTSS-10 to determine whether screening 1 week after weaning would identify patients at risk of PTSD 3 months later.	**10 questionnaires to evaluate the presence and intensity of 10 posttraumatic stress symptoms:** 1. sleep disturbance 2. nightmares 3. depression 4. jumpiness 5. wishing to withdraw from others 6. generalized irritability 7. frequent changes in mood 8. guilt 9. fear of places and situations that remind the patient of the time of weaning 10. increased muscle tension Rated from 1 (never) to 7 (always); the total score ranges from 10 to 70 **4 additional yes or no questions regarding stressful memories during weaning:** 1. breathing difficulty 2. panic or anxiety 3. pain 4. nightmares	Self-reported Via telephone	Structured Clinical Interview (SCID)	***Reliability:*** Not reported ***Validity:*** • Comparison of PTSS-10 scores at enrollment with SCID (3 months after weaning), area under the receiver operating characteristic (AUROC) curve=0.91 ***Sensitivity:*** Sensitivity of 1.0 (PTSS 10 score>20) ***Specificity:*** 0.76 (95% CI 0.56–0.89) ***positive-predictive value***=0.36 (95% CI 0.08–0.65) ***negative-predictive value***=1.0 ***likelihood ratio***=4.1 (95% CI 1.5–7.5)
Stoll et al., 1999	Post-traumatic stress syndrome questionnaire (PTSS-10) PTSD in ARDS survivors	Modified original Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10) Item 9 of the original questionnaire was changed from "fears when approaching the place of the	**2 parts:** **Part A: Assessment of traumatic memories from the intensive care unit** 1. Nightmares 2. Severe Anxiety or Panic 3. Severe Pain 4. Troubles to breath, feelings of suffocation yes or no type questions **Part B: post-traumatic stress disorder symptoms**	Self-reported Send questionnaires to participants	Structured Clinical Interview for DSM-IV (SCID)	***Reliability:*** ***Internal consistency,*** • Cronbach's α = 0.91 (first measurement) AND 0.93 (second evaluation) ***Test-Retest reliability,*** • intraclass correlation = 0.89 (F = 9.24, 95% confidence interval: 0.81±0.94) ***Validity:*** ***construct validity*** • Relationship between traumatic memories and scores on the

		accident or situations that reminded me of it" to "fear of places and situations, which remind me of the intensive care unit" To maintain the context between traumatic memories from the ICU and the development of PTSD symptoms 4 additional yes or no questions regarding stressful memories from the intensive care unit were added	10 PTSD symptoms: 1. sleep disturbance 2. nightmares 3. depression 4. hyperalertness, 5. withdrawal (emotional numbing and inability to care for others) 6. generalized irritability 7. frequent changes in mood 8. guilt 9. avoidance of activities prompting the recall of possible traumatizing events 10. increased muscle tension 7-point Likert scale ranging from 1 (never) to 7 (always). The total score of the questionnaire is calculated as the sum scores of all 10 items			questionnaire, Spearman's $r = 0.48$, $p < 0.01$ ***Criterion validity*** • 10 of 13 patients in the sample who had PTSD according to SCID were correctly identified by PTSS-10. • 39 patients did not have PTSD according to SCID and 38 of these patients were correctly identified (1 false positive) by PTSS-10. ***Sensitivity: 77.0%*** (95% confidence interval 54±100%) (threshold value of 35 points) ***Specificity:*** 98% (95% confidence interval 91±100%) ***positive predictive value***= 93% (95% confidence interval 85±100%) ***Accuracy***= 92%
Twigg et al., 2008	UK Post-traumatic stress syndrome 14-questions inventory (UK-PTSS-14) PTSD in ICU survivors	Modified the PTSS-10 based on the diagnostic criteria for PTSD DSM-IV: increased arousal, reexperiencing, and avoidance/numbing by the research team, consisting of multidisciplinary experts in the field of PTSD assessment and treatment PTSS-10 has no items related to numbing or flashbacks, and only one directly linked with	**14 items:** 1. Sleep problem 2. Nightmares 3. Depression 4. Jumpiness 5. The need to withdraw from others 6. Irritability 7. Frequent mood swings 8. guilt feelings 9. Fear of places and situations reminding intensive care unit 10. Muscular tension 11. Upsetting, unwanted thoughts or images of time on the intensive care unit 12. Feeling numb 13. Avoid places, people or situations that remind of the intensive care unit 14. Feeling as if plans or dreams for the future will not come true Rated on 7-point Likert scale from 1 (never) to 7	Self-reported verbally/telephone Administered by the researcher	Post Diagnostic Scale (PDS) Impact of Events Scale (IES)	***Reliability:*** ***Internal consistency***, • Cronbach's $\alpha = 0.89$ (4–14 days post-discharge), 0.86 (2 months post-discharge) and 0.84 (3 months post-discharge) ***Test–retest reliability***, • intraclass correlation coefficient (ICC) across time-points: o two and three, ICC=0.90 o one and two, ICC=0.77 o one and three, ICC=0.70 ***Validity:*** ***Concurrent validity,*** Correlation between UK-PTSS-14 score at 3 months post-discharge and: o PDS, Pearson's correlation=0.86 o IES, Pearson's correlation=0.71

		avoidance (i.e., item 5: 'Need to withdraw from others'). Therefore, added four additional items to measure these omissions.	(always), summed with equal weighting to derive a total score ranging from 14 to 98.			***Predictive validity***, • Time-point 1 (4–14 days), Pearson's correlation =0.50 (CI=0.24–0.69) with PDS at 3 months and 0.44 (CI=0.17–0.65) with IES at 3 months • Time-point 2 (2 months) Pearson's correlation = 0.85 (CI=0.74–0.92) with PDS at 3 months and 0.71 (CI=0.52–0.83) with IES at 3 months ***Sensitivity:*** • 4–14 days=71% (CI=29.3–95.5) • 2 months=86% (CI=42.2–97.6) • 3 months=100% (CI=58.9–100.0) ***Specificity:*** • 4–14 days=84% (CI=68.0–93.8) • 2 months=97% (CI=85.8–99.5) • 3 months=84% (CI=68.0–93.8)
Rosendahl et al., 2019	Post-traumatic stress syndrome questionnaire (PTSS-10) Post-traumatic stress syndrome questionnaire (PTSS-14) Posttraumatic Stress Disorder Checklist (PCL-5) PTSD in ICU survivors	Compared PTSS-10, PTSS-14, and PCL-5 to rule out which is more appropriate for post-ICU PTSD screening and when validated against a DSM-5 diagnostic interview	PTSS-10 measures 10 common PTSD symptoms Rated using a 7-point Likert scale (1 = never; 7 = always) PTSS-14 is extended version of PTSS-10, includes additional 4 items: numbing or flashbacks, and avoidance Rated using 7-point Likert scale (1 = never; 7 = always) PCL-5 focuses on 20 points of measure for PTSD	self-reported administered by research assistant who was trained and supervised by a clinical psychologist	Clinical Administered PTSD Scale for DSM-V (CAPS-5)	***Reliability:*** ***Internal consistency,*** • Cronbach's α = 0.83 for PTSS-10, 0.88 for PTSS-14, 0.92 for PCL-5 ***Validity:*** ***Concurrent validity,*** • Correlated with the CAPS-5 total symptom severity score; PTSS-10: ρ =0.77, PTSS-14: ρ=0.82, PCL-5: r=0.90 (p= 0.001 for all instruments). • between the three measures, PTSS-10 and PCL-5, r = 0.82, PTSS-14 and PCL-5, r = 0.85, and PTSS-10 and PTSS-14, r = 0.98 (p b 0.001). ***Criterion validity,*** • for all three screening instruments, AUC> 0.90 ***Convergent validity*** • Scores of all three screening instruments (at T2) were associated with psychological

						comorbidities and health-related quality of life ***Sensitivity:*** PTSS-10=60%, PCL-5=50%, and PTSS-14=80% ***Specificity:*** PTSS-10=95.9%, PTSS-14=91.8% and PCL-5= 95.9% ***Positive predictive value (PPV):*** 66.7%, 57.1%, and 62.5% for PTSS-10, PTSS-14, and PCL-5 respectively ***Negative predictive value (NPV):*** 94.6%, 97.1%, and 93.3% for PTSS-10, PTSS-14, and PCL-5 respectively
Kentish-Barnes et al., 2016	CAESAR PTSD and complicated grief	**Initial questionnaire developed from**: A review of the medical, nursing, and social science Literature. The experience accumulated by the research group. In-depth qualitative interviews by a sociologist with relatives of patients expected to die in the ICU, bereaved relatives, physicians, and nurses. A panel of 10 investigators (5 physicians, 2	**15-item questionnaire and 3 domains** 1. The patient (preparation for death, whole person concerns, symptoms, personal care, and treatment preferences) 2. Interactions with and around the patient (Quality of communication between the ICU team and the patient and ICU team and the relatives, particularly whether conflicts arose) 3. Family needs and satisfaction **Measurement:** both a written description and a score on a 5-point scale (1, traumatic; 2, painful; 3, difficult; 4, acceptable; and 5, comforting).	Self-reporting Via telephone same sociologist with extensive interviewing experience 20 min	HADS IES-R	***Reliability:*** • Cronbach's α =0.88 (0.85–0.90) and 0.85 (0.79–0.89) in the main and reliability cohorts respectively ***Validity:*** • Factorial analysis confirmed good construct validity ***Sensitivity:*** Not reported ***Specificity:*** Not reported

		nurses and 3 sociologists/psychologists) identified 8 domains and 50 items about the experience of relative. The items were then tested twice with relatives of patients, as well as with physicians and nurses, in one ICU. 17 items were eliminated after the distribution of each item was examined, and factorial analysis was performed to identify items with a weak representation. 18 additional items were eliminated because they were redundant.				

Tool psychometric properties

Validity: Adequate validity metrics in assessing PTSD/PICS in ICU survivors/family caregivers are reported for most tools, except for OMI set to assess PICS (Spies, et al., 2019) (see table 3).

Tools for PICS

Two out of five PICS tools depicted acceptable validity to access PICS in ICU survivors. PICSQ (Jeong et al., 2019) demonstrated good criterion, construct, convergent, and discriminant validity. Similarly, RAIN revealed excellent convergent validity. In addition, content validity

index and discriminant validity figures were satisfactory (Bergbom et al., 2018). Conversely, HABC-M SR (Wang et al., 2019) demonstrated limited construct validity. Particularly, the HABC-M cognitive scale demonstrated low correlations with the cognitive performance measures. The 3-Set 4P Questionnaire (Akerman et al., 2009 and Akerman et al., 2012) demonstrated good construct validity, while the concurrent validity figures were acceptable.

All of the QOL assessment tools confirmed validity in ICU survivors. SIP (Tian and Miranda, 1994) demonstrated acceptable construct validity and authors found the SIP structure in patients after intensive care and the original paper in patients with hyperthyroidism, rheumatoid arthritis, and hip replacements similar. Another tool, PQOL, demonstrated acceptable construct validity**.** SF-36 (Chrispin 1996; Heyland et.al., 2000; Khoudri et al.,2007) demonstrated acceptable construct validity when compared with PQOL. EQ-5D (Khoudri et al., 2012) showed evidence of criterion and construct validity. However, comparing EQ-5D and RAND revealed that both the tools correlated well, but discriminatory power of the EQ-5D was weaker than RAND particularly with Mobility, Self-Care, and lower QOL values.

Tools for Physical Impairments

Overall, five tools demonstrated evidence of validity for physical impairment post-ICU, whereas measures of validity were weak in another two tools. Specifically, CPAx showed good construct validity to assess physical impairment in ICU survivors (Corner et al., 2012; Corner et al., 2014). The CPAx demonstrated excellent content validity and has a limited floor-and-ceiling effect to detect functional change throughout critical illness, implying usefulness in monitoring patients' functional recovery overtime. 6MWD (Chan et al., 2015) demonstrated evidence of good convergent and discriminant validity. In addition, it had good predictive validity for future mortality, rehospitalization, survival, return to normal activity, and HRQL. The predictive

screening instrument (Schandl, 2014) showed fair predictive validity to assess the patient's individual risk for new-onset physical disability two months after ICU stay. Both the BI and the KI (Da Silveira et al., 2018) revealed adequate measurement validity to assess deterioration of functional status after ICU discharge. However, the item response theory analysis suggested that the BI might be a better scale than the KI for the assessment of functional status in this population. CFQ-14 (Wassenaar et al., 2018) correlated highly with the original 25-item CFQ. The ICU discharge screening tool for prediction of new-onset physical disability (Milton et al., 2019) demonstrated moderate predictive validity. Conversely, MFI-20 (Wintermann et al., 2018) demonstrated low validity.

Tools for Cognitive Impairments

The telephone battery (Christie et al, 2006) showed good construct validity and correlation with in-face interviews, excluding the Hayling Sentence Completion Test and the WMS-III Letter-Number Sequencing Test. FACT-Cog $_{\text{adapted}}$ (Baumbach et al., 2016) showed good-excellent convergent and divergent validity. However, two other tools showed only moderate validity for the assessment of neurocognitive impairments. Specifically, MMSE 26-item scores (Pfoh et al., 2015) were weakly to moderately correlated with neuropsychological tests, and had fair discrimination in detecting cognitive impairment at 6 and 12 months but not at 3 months. Similarly, MoCA (Brown et al., 2018) corresponded moderately with the neuropsychological test battery with fair discrimination only at 6 months in sepsis survivors (Brown et al., 2018).

Tools for Mental Health Impairments and PTSD

Most of the tools illustrated evidence of validity to assess mental health impairment in ICU survivors. HADS (Jutte et al., 2015) depicted good convergent validity. In addition, AUC analysis confirmed predictive validity to assess anxiety and depression three months after ICU discharge

(Milton et al., 2017). Similarly, DASS (Sukantarat et al., 2007) showed good criterion validity. The psychological risk prediction instrument (Milton et al., 2018) demonstrated good predictive validity to triage ICU survivors for psychological impairment during ICU follow-up. Likewise, the predictive screening instrument (Schandl et al., 2013) showed fair validity in discriminating patients with poor psychological recovery.

CDTS-I-T (Karanikola et al., 2020), through factor analysis, confirmed good construct validity. ETIC-7 (Scragg, et al., 2000) demonstrated good concurrent validity when correlated with IES and TSC-33 scores, as well as HADS-A. Similarly, IES-6 (Hosey et al., 2019) had stronger correlations with mental health, anxiety, and depression over time demonstrating construct validity. In addition, IES-6 reported good criterion validity. IES-R (Bienvenu et al., 2013) demonstrated good discriminant and concurrent validity. PTSS-10 demonstrated evidence of construct and criterion validity in ARDS survivors (Stoll, et al., 1999) and general ICU survivors (Milton et al., 2017). However, when examining survivors of mixed ICU, PTSS-10 diagnosed twice as many PTSD cases compared to SCID (Nickel et al., 2004). The ROC determined good predictive validity of the PTSS-10 in patients who were weaned from prolonged ventilation (Jubran et al., 2010). The UK-PTSS-14 (Twigg et al., 2008) showed acceptable levels of concurrent validity when correlated with the IES and PDS at 3 months post ICU. In addition, the UK-PTSS-14 showed good levels of predictive validity taken at 2 months. All three tools, PTSS-10, PTSS-14, and PCL-5 (Rosendahl et al., 2019), revealed good concurrent, criterion and convergent validity. Although PTSS-14 was developed according to DSM-IV diagnostic criteria of PTSD, it performed well in making provisional PTSD diagnosis in reference to the most current Diagnostic Manual of Mental Disorders (DSM-5) compared to PTSS-10 and PCL-5. The PCL-C

sleep item score correlated significantly with ISI score, suggesting criterion validity, and correlation with QOL indices indicated construct validity (Parsons et al., 2018).

Tools for PICS- Family

CAESAR (Kentish-Barnes et al., 2016) demonstrated good construct validity to assess the experience of relatives of patients who die in the ICU. Furthermore, a low CAESAR score was associated with greater risks of anxiety and depression at 3 months, PTSD-related symptoms at 3 and 12 months, and complicated grief at 6 months. Another tool, FACT-Cog $_{\text{adapted}}$ (Baumbach et al., 2016) showed significant spearman rank correlation coefficients with the scores of the validated IQCODE.

Reliability: In most studies the authors examined, the reliability of internal consistency using pre-set criteria for Cronbach's alpha coefficient between 0.70-0.95. In addition to internal consistency reliability, few studies assessed inter-rater reliability (Brown et.al., 2018; Christie et.al, 2006; Corner et al., 2012; Milton et al., 2019; Pfoh et.al., 2015; Schandl 2014). Similarly, 4 studies assessed test-retest reliability (Akerman, et al., 2009; Akerman, et al., 2012; Chrispin 1996; Jeong, et al., 2019; Karanikola et al., 2020; Stoll et al., 1999; Twigg et al., 2008). However, in several studies the reliability of the tool was not assessed (table 3).

PICS Tools

In precis, five tools: Recovery After INtensive Care (RAIN), 3-Set 4P Questionnaire, HABC-M SR, and PICSQ demonstrated evidence of internal consistency. RAIN instrument showed good internal consistency in surgical, medical and trauma survivors. HABC-M SR demonstrated good to excellent internal consistency for each factor in general ICU survivors; 3-Set 4P Questionnaire revealed good internal consistency and test-retest reliability in mixed ICU survivors. PICSQ demonstrated good internal consistency and high test-retest reliability.

Among the quality-of-life assessment tools: SF-36, PQOL, and EQ-5D demonstrated acceptable internal consistency in medical, surgical, or mixed ICU survivors. In addition, SF-36 revealed good test-retest reliability, whereas both Arabic version of EQ-5D and SF-36 showed excellent test-retest reliability in medical ICU survivors.

Tools for Cognitive Impairments

Similarly, five tools demonstrated good reliability in the measurement of cognitive impairment in ICU survivors. Two of these tools, CFQ-14 and FACT-Cog $_{\text{adapted}}$, demonstrated good internal consistency in surgical and mixed ICU survivors. Both MMSE 26-item Version and MoCA demonstrated low inter-rater reliability.

Tools for Physical Impairments

Four tools demonstrated evidence of reliability in assessing functional status in ICU survivors. The predictive screening instrument demonstrated excellent inter-rater agreement (>0.9). ICU discharge screening tool for prediction of new-onset physical disability demonstrated acceptable inter-rater reliability. More specifically, moderate for cough, supine to sitting and moving within the bed items; substantial for dynamic sitting; and almost perfect for respiratory function. CPAx demonstrated excellent inter-rater reliability and acceptable internal consistency in medical, surgical and trauma ICU survivors. MFI-20 showed acceptable internal consistency in patients after prolonged intensive care treatment. Particularly, the subscale Reduced Motivation (RM) revealed inadequate value (Cronbach's $\alpha = .50$). However, corrected item-to-total and inter-item correlation showed inadequate values for the MFI-total and the RM subscale (values< .30).

Tools for Mental Health Impairments & PTSD

Only two tools, DASS and HADS, demonstrated good internal consistency for determining psychological impairment in general ICU survivors. However, eight tools – Cypriot version of

DTS-I-M, ETIC-7, IES-6, PTSS-14, IES-R, PTSS-10, and UK-PTSS-14 – showed good internal consistency to assess PTSD in mixed ICU survivors. In addition, Cypriot version of DTS-I-M, PTSS-10, and UK-PTSS-14 also demonstrated good test-retest reliability.

Tools for PICS- Family

CAESAR and FACT-Cog $_{adapted}$ showed good internal consistency to assess PTSD and complicated grief in family caregivers of patients who died in the ICU, and cognitive impairment in families of ICU survivors, respectively.

Diagnostic accuracy: Several studies reported on the diagnostic accuracy of the tools under study using specificity, sensitivity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) figures. However, none of the physical impairment assessment tools were investigated regarding their diagnostic accuracy in ICU survivors.

Tools for PICS

Out of 5 PICS tools, only PICSQ (Jiyeon et al., 2020) demonstrated good sensitivity (85.5%) and specificity (80.9- 81.5%) in assessment of PICS in ICU survivors.

Tools for Cognitive Impairments

Based on the evidence both MMSE and MoCA performed poorly when assessing cognitive impairment in ICU survivors. MMSE 26-item Version (Pfoh et al 2015) showed poor sensitivity and NPV, but high specificity and Positive Predictive Value PPV. In contrast, MoCA (Brown et al 2018) showed good sensitivity (92%) but poor specificity (71%).

Tools for Mental Health Impairments and PTSD

The screening method (Milton et al., 2019) showed satisfactory sensitivity (73%), specificity (60%), and NPV (88%) but low PPV (32%). HADS (Jutte et al., 2015; Milton et al., 2017) demonstrated acceptable sensitivity (HADS-A=77-82%, HADS-D=73%), specificity

(HADS-A=65-72%,HADS-D=57-60%), and NPV (HADS-A=95%, HADS-D=91%), but poor PPV (HADS-A=37%, HADS-D=37%). The psychological risk prediction instrument for use at ICU discharge (Milton et al., 2018) showed good PPV (83%), and NPV (84%).

Similarly, PTSS-10 (Jubran et al., 2010; Milton et al., 2017; Stoll et al., 1999) demonstrated satisfactory sensitivity (77-100%), specificity (76-98%), PPV (50-95%), and NPV (98%). IES-6 (Hosey et al., 2019) demonstrated satisfactory sensitivity (88%), specificity (85%), and NPV (98%), but poor PPV (47%). IES-R (Bienvenu, et al., 2013) showed good sensitivity (80-100%), specificity (85-91%), and NPV (93-100%) but low PPV (50-75%). Similarly, PTSS-14 (Rosendahl et al., 2019) showed satisfactory sensitivity (80%), specificity (91.8%), and NPV (97.1%), but low PPV (57.1%). UK-PTSS-14 (Twigg et al., 2008) demonstrated satisfactory sensitivity (71%, 86%, 100%), and specificity (84%, 97%, 84%) to assess PTSD at 4–14 days, 2 months, and 3 months, respectively. Similarly, PCL-5 (Rosendahl et al., 2019) revealed satisfactory specificity (95.9%), and NPV (93.3%) but low sensitivity (50%) and PPV (62.5%). Altogether, data suggests that PTSS-10, PTSS-14, and PCL-5 are clinically useful screening tools for PTSD in patients after intensive care. However, when using the recommended cut-off values for provisional PTSD diagnosis, all measures showed high specificity but only PTSS-14 revealed an acceptable sensitivity (Rosendahl, et al., 2019). PCL-C sleep item (Parsons, et al., 2018) demonstrated good sensitivity (91%), and NPV (95%), but low specificity (67%) and PPV (51%).

Discussion

PICS is a significant long-term complication following critical illness for patients as well as their families, globally. One of the challenges in identifying patients with, or at risk for, PICS is the need for standardised tools addressing all three domains (physical, mental, and cognitive) of

PICS symptomatology (Mikkelsen et al., 2020). This study aimed to address the metric properties and methodological issues of PICS and PTSD assessment tools used in practice and research.

The main findings of this review include: a) a limited number of tools addressing all three domains of PICS; b) unclear validity of the tools in the post-ICU population, especially for the recommended timeframe of assessment at 2-4 weeks post-discharge; c) limitations with some tools' feasibility in the post-ICU population; d) low diagnostic accuracy of cognitive assessment tools; e) evidence of appropriate psychometric properties and feasibility of psychological health assessment tools; and g) only two tools addressing PICS in families of ICU survivors. One limitation of this review was the exclusion of non-English published articles that may have contained important findings to inform PICS research.

Our review identified only five tools that could assess all three domains of PICS: PISC-Q, HABC-M-SR, RAIN, OMI set, and the provisional questionnaire for long-term health-related quality of life and burden of disease after intensive care. Moreover, the OMI set tool used a combination of cognitive, mental, and physical screening tools for initial and extended screening (Spies et al., 2021). A potential limitation of OMI set lies with the number of tools employed to measure PICS, as using several tools can be time-intensive and may require additional training. Conversely, a brief tool for initial first triage, such as PICS-Q and RAIN, can not only be quick and easier to administer, but may also result in a better response rate. Subsequently, in-depth evaluation for suspected cases can be done with extensive tools for each domain on the later stage (Mikkelsen et al., 2020; Spies et. al., 2021).

Our review highlighted concerns regarding the validity and appropriateness of the tools to use, especially if they have been developed and tested in populations that are atypical of the post-ICU population. The current review additionally shows that most of the existing tools have

limitations worth considering in future developments, such as size and representativeness of the post-ICU sample where they were tested. Similarly timing of assessment was another area of concern. The Society of Critical Care Medicine recommends serial assessments for PICS-related problems within 2–4 weeks of hospital discharge (Mikkelsen et al., 2020). Only a few tools, HADS, BI and PTSS-14, showed acceptable metric properties within this timeframe (Da Silveira et al., 2018; Milton et al., 2017; Twigg et al., 2008; Wang et al., 2019; Warlan et al., 2016). Other tools were either not appropriate or not tested at that timepoint, as the majority of assessments took place between 2 and 12 months post-ICU. Moreover, most metric analyses were done during the development phase of the tools. Therefore, additional investigations are needed to establish the internal consistency, stability, and validity of these tools in larger populations and on longitudinal follow-up. Moreover, few tools did not use gold standard tools for testing the validity and diagnostic accuracy (Bergbom et al., 2018; Chrispin 1996; Corner et al., 2014; Kang et al., 2020; Malmgren et al., 2021; Milton et al., 2017; Tian and Miranda, 1994), which further mandates the need for comprehensive validation in ICU survivors and their families.

Our review shows that evidence regarding the available tools' feasibility is mostly inconclusive, with lengthy instruments contributing to testing burden. The results reviewed herein, confirm that the length of instruments, reading ability of patients, completion time, and method of administration are all important considerations when selecting a tool for PICS/PTSD assessment in ICU survivors/families, along with issues of validity and reliability in the target population.

Issues of diagnostic accuracy are also worth noticing. Only PICS-Q showed acceptable diagnostic accuracy to assess PICS in ICU survivors. However, none of the cognitive impairment assessment tools except the telephone version of neuropsychological test demonstrated diagnostic accuracy for ICU survivors. For instance, MMSE, one of the common cognitive screening tools,

demonstrated fair agreement and poor sensitivity when compared to neuropsychological test batteries in acute respiratory failure survivors during their first year of recovery. MoCA, which is recommended for cognitive assessment in ICU survivors (Mikkelsen et al., 2020; Spies et al., 2021), corresponded modestly with neuropsychological test battery among sepsis survivors and depicted fair sensitivity but poor specificity at 6 months in sepsis survivors. Likewise, none of the physical impairment assessment tools evaluated their diagnostic accuracy. 6MWD, which is suggested as one of the core outcome measures for physical impairment in ICU survivors, showed evidence of acceptable validity and reliability along with excellent predictive validity for future mortality, rehospitalization, survival, return to normal activity, and HRQL. Additionally, CPAx, BI, KI and CFQ-14 demonstrated good validity in ICU survivors.

Most of the identified tools provided promising results for detecting psychological impairment and PTSD among ICU survivors. Moreover, these tools can be administered to patients without engaging a psychologist or psychiatrist. Most tools assessed patients from general ICUs, thus, are generalizable to a wider ICU population. In line with the recommendation by the Society of Critical Care Medicine (2020), our analysis also showed superiority of HADS to identify anxiety and depression in ICU survivors. Our review revealed that IES-6 is the briefest measure of PTSD symptoms validated in ICU survivors. IES-R was recently recommended as core outcome measure in ICU survivors (Mikkelsen et al., 2020; Spies et.al., 2021). However, our analysis suggests the IES-6, compared to IES-R, could improve efficiency while maintaining adequate measurement properties in screening for PTSD symptoms.

Our review also identified some tools solely developed to predict patients at risk for PICS after critical illness. The Provisional questionnaire for long-term health-related quality of life and burden of disease after intensive care (Malmgren et al., 2021) placed some groundwork to identify

patients at risk for PICS. Similarly, the psychological risk prediction instrument (Milton et al., 2018) and the predictive screening instrument (Schandl et al., 2013) showed fair validity in predicting the patient's individual risk for new-onset physical disability. Similarly, ICU discharge screening tool for prediction of new-onset physical disability (Milton et al., 2019) and the predictive screening instrument (Schandl, 2014) showed fair predictive validity to assess the patient's individual risk for new-onset physical disability after ICU stay. However, more research with larger sample sizes is needed for conclusive results.

Our review identified only two tools – CAESAR and FACT-Cog $_{\text{adapted}}$ – validated in families of ICU survivors/patients. The relative scarcity of studies employing PICS/PTSD assessment instruments in the families of ICU survivors is worth noting. Our review demonstrates that PICS-F/PTSD-F receives very low priority, and thereby challenges the assessment of relevant topics in families of critically ill patients. Similarly, a recent systematic review on interventions for PICS-F identified only three studies focused on post-discharge period interventions and recognized the paucity of research associated with families of ICU survivors (Zante et al., 2020). The review also highlighted inconsistencies among studies in use of screening tools to assess PICS-F. Recently, the Society of Critical Care Medicine (2018) highlighted the importance of family engagement and recommended guideline on how to involve families in the care of ICU patients. However, the guideline failed to acknowledge the impact on PICS-F and thus did not include any recommendation on screening tools for PICS-F, specific time to administer these screening tools, or responsible disciplines for assessing and managing PICS-F (Pun et al., 2018).

Conclusion and Implications

Post-discharge care for ICU survivors is fragmented relying on primary care physicians or post-ICU clinics for follow-up. Key issues underlying inadequate diagnosis and treatment of PICS

is the lack of routine post-hospital follow-up, absence of specialized clinics or personnel in most cases, and clarity as to who bears the responsibility for post-ICU follow-up, ICU clinics or primary care providers (Colbenson et al., 2019; Rousseau et al., 2021). As a result, most ICU survivors continue to receive their care from primary care physicians or outpatient physicians who lack awareness that PICS exists and is relatively common among ICU survivors. Furthermore, there are no established best practice guidelines on how to best treat and support ICU survivors (Colbenson et al., 2019; Needham et al., 2012). Therefore, a brief screening tool that can be used by healthcare professionals with little expertise to rapidly screen ICU survivors during follow-up may prove useful to identify major targets for intervention and individuals at risk. This study set out to evaluate the metric properties, and appropriateness and feasibility of available PTSD/PICS assessment tools in ICU survivors and their families. We identified the absence of a PICS/PTSD assessment tool for family caregivers of ICU survivors as a significant gap. We highlighted gaps in the literature that need to be addressed to promote meaningful clinical outcomes. Also, there is a need to examine whether primary care practitioners can accurately administer the tools for ICU survivors, and subsequently diagnose and refer for the management.

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Reference

Akerman, E., Fridlund, B., Ersson, A., & Granberg-Axéll, A. (2009). Development of the 3-SET 4P questionnaire for evaluating former ICU patients' physical and psychosocial problems over time: a pilot study. *Intensive & critical care nursing*, *25*(2), 80–89. https://doi.org/10.1016/j.iccn.2008.06.004

Akerman, E., Fridlund, B., Samuelson, K., Baigi, A., & Ersson, A. (2013). Psychometric evaluation of 3-set 4P questionnaire. *Intensive & critical care nursing*, *29*(1), 40–47. https://doi.org/10.1016/j.iccn.2012.06.002

American Psychological Association. (2017). Clinical practice guideline for the treatment of posttraumatic stress disorder (PTSD) in adults. Retrieved from: https://www.apa.org/ptsd-guideline

Amra, S., John C., O., Mikhail, D., Dziadzko, V., Rashid, A., Tarun D., S., Rahul, K., Ann M., F., John D., F., Ronald, P., Ognjen, G., & Alejandro A., R. (2018). Potentially Modifiable Risk Factors for Long-Term Cognitive Impairment After Critical Illness: A Systematic Review. *Mayo Clinic Proceedings*, *93*(1), 68–82.

Annachiara, M., Pratik P., P., Timothy D., G., Mayur B., P., Christopher G., H., James C., J., Jennifer L., T., Rameela, C., Eugene Wesley, E., & Nathan E., B. (2018). Co-Occurrence of Post-Intensive Care Syndrome Problems Among 406 Survivors of Critical Illness*. *Critical Care Medicine*, *46*(9), 1393–1401. https://doiorg.login.ezproxy.library.ualberta.ca/10.1097/CCM.0000000000003218

Appleton, R. T., Kinsella, J., & Quasim, T. (2015). The incidence of intensive care unit-acquired weakness syndromes: A systematic review. *Journal of the Intensive Care Society*, *16*(2), 126–136. https://doi.org/10.1177/1751143714563016

Baumbach, P., Götz, T., Meissner, W., Guenther, A., & Witte, O. W. . (n.d.). Perceived cognitive impairments after critical illness: a longitudinal study in survivors and family member controls. *Acta Anaesthesiologica Scandinavica*, *60*(8), 1121–1130. https://doi /10.1111/aas.12755

Bergbom, I., Karlsson, V., & Ringdal, M. (2018). Developing and evaluating an instrument to measure Recovery After INtensive care: the RAIN instrument. *BMC nursing*, *17*, 5. https://doi.org/10.1186/s12912-018-0275-1

Bienvenu, J. O., Williams, J. B., Yang, A., Hopkins, R. O., & Needham, D. M. (2013). Posttraumatic Stress Disorder in Survivors of Acute Lung Injury: Evaluating the Impact of Event Scale-Revised. *Chest*, *144*(1), 24–31. https://doi /10.1378/chest.12-0908

Brown, S. M., Collingridge, D. S., Wilson, E. L., Beesley, S., Bose, S., Orme, J., Jackson, J., & Hopkins, R. O. (2018). Preliminary Validation of the Montreal Cognitive Assessment Tool among Sepsis Survivors: A Prospective Pilot Study. *Annals of the American Thoracic Society*, *15*(9), 1108–1110. https://doi.org/10.1513/AnnalsATS.201804-233OC

Chan, K. S., Pfoh, E. R., Denehy, L., Elliott, D., Holland, A. E., Dinglas, V. D., & Needham, D. M. (2015). Construct validity and minimal important difference of 6-minute walk distance in survivors of acute respiratory failure. *Chest*, *147*(5), 1316–1326. https://doi.org/10.1378/chest.14-1808

Chrispin, P. S., Scotton, H., Rogers, J., Lloyd, D., & Ridley, S. A. (1997). Short Form 36 in the intensive care unit: assessment of acceptability, reliability and validity of the questionnaire. *Anaesthesia*, *52*(1), 15–23.

Christie, J. D., Biester, R. C., Taichman, D. B., Shull, W. H., Jr, Hansen-Flaschen, J., Shea, J. A., & Hopkins, R. O. (2006). Formation and validation of a telephone battery to assess

cognitive function in acute respiratory distress syndrome survivors. *Journal of critical care*, *21*(2), 125–132. https://doi.org/10.1016/j.jcrc.2005.11.004

Colbenson, G. A., Johnson, A., & Wilson, M. E. (2019). Post-intensive care syndrome: impact, prevention, and management. *Breathe (Sheffield, England)*, *15*(2), 98–101. https://doi.org/10.1183/20734735.0013-2019

Corner, E. J., Soni, N., Handy, J. M., & Brett, S. J. (2014). Construct validity of the Chelsea critical care physical assessment tool: an observational study of recovery from critical illness. *Critical care (London, England)*, *18*(2), R55. https://doi.org/10.1186/cc13801

Corner, E. J., Wood, H., Englebretsen, C., Thomas, A., Grant, R. L., Nikoletou, D., & Soni, N. (2013). The Chelsea critical care physical assessment tool (CPAx): validation of an innovative new tool to measure physical morbidity in the general adult critical care population; an observational proof-of-concept pilot study. *Physiotherapy*, *99*(1), 33–41. https://doi.org/10.1016/j.physio.2012.01.003

Davidson, J. E., Jones, C., & Bienvenu, O. J. (2012). Family response to critical illness: postintensive care syndrome-family. *Critical Care Medicine*, *40*(2), 618–624. https://doi.org/10.1097/CCM.0b013e318236ebf9

Desai, S. V., Law, T. J., & Needham, D. M. (2011). Long-term complications of critical care. *Critical Care Medicine*, *39*(2), 371–379. https://doi.org/10.1097/CCM.0b013e3181fd66e5

Harlan, E. A., Miller, J., Costa, D. K., Fagerlin, A., Iwashyna, T. J., Chen, E. P., Lipman, K., & Valley, T. S. (2020). Emotional Experiences and Coping Strategies of Family Members of Critically Ill Patients. *Chest*, *158*(4), 1464–1472. https://doi.org/10.1016/j.chest.2020.05.535

Heyland, D. K., Hopman, W., Coo, H., Tranmer, J., & McColl, M. A. (2000). Long-term health-related quality of life in survivors of sepsis. Short Form 36: a valid and reliable measure of health-related quality of life. *Critical care medicine*, *28*(11), 3599–3605. https://doi.org/10.1097/00003246-200011000-00006

Hosey, M. M., Leoutsakos, J. S., Li, X., Dinglas, V. D., Bienvenu, O. J., Parker, A. M., Hopkins, R. O., Needham, D. M., & Neufeld, K. J. (2019). Screening for posttraumatic stress disorder in ARDS survivors: validation of the Impact of Event Scale-6 (IES-6). *Critical care (London, England)*, *23*(1), 276. https://doi.org/10.1186/s13054-019-2553-z

Jeong, Y. J., & Kang, J.. (n.d.). Development and validation of a questionnaire to measure post-intensive care syndrome. *Intensive and Critical Care Nursing*, *55*. https://doi /10.1016/j.iccn.2019.102756

Jezierska N. (2014). Psychological reactions in family members of patients hospitalised in intensive care units. *Anaesthesiology Intensive Therapy*, *46*(1), 42–45. https://doi.org/10.5603/AIT.2014.0009

Jubran, A., Lawm, G., Duffner, L. A., Collins, E. G., Lanuza, D. M., Hoffman, L. A., & Tobin, M. J. (2010). Post-traumatic stress disorder after weaning from prolonged mechanical ventilation. *Intensive Care Medicine*, *36*(12), 2030–2037. https://doi /10.1007/s00134-010-1972-8

Jutte, J. E., Needham, D. M., Pfoh, E. R., & Bienvenu, O. J. (2015). Psychometric evaluation of the Hospital Anxiety and Depression Scale 3 months after acute lung injury. *Journal of critical care*, *30*(4), 793–798. https://doi.org/10.1016/j.jcrc.2015.04.006

Kaarlola, A., Pettilä, V., & Kekki, P. (2004). Performance of two measures of general health-related quality of life, the EQ-5D and the RAND-36 among critically ill patients. *Intensive care medicine*, *30*(12), 2245–2252. https://doi.org/10.1007/s00134-004-2471-6

Kang, J., Jeong, Y. J., & Hong, J. (2020). Cut-Off Values of the Post-Intensive Care Syndrome Questionnaire for the Screening of Unplanned Hospital Readmission within One Year. *Journal of Korean Academy of Nursing*, *50*(6), 787–798. https://doi.org/10.4040/jkan.20233

Karanikola, M., Alexandrou, G., Mpouzika, M., Chatzittofis, A., Kusi, A. E., & Papathanassoglou, E. (2021). Pilot exploration of post-traumatic stress symptoms in intensive care unit survivors in Cyprus. *Nursing in Critical Care*, *26*(2), 109–117. https://doi /10.1111/nicc.12574

Kentish-Barnes, N., Seegers, V., Legriel, S., Cariou, A., Jaber, S., Lefrant, J.-Y., Floccard, B., Renault, A., Vinatier, I., Mathonnet, A., Reuter, D., Guisset, O., Cracco, C., Seguin, A., Durand-Gasselin, J., Éon, B., Thirion, M., Rigaud, J.-P., Philippon-Jouve, B., … Azoulay, E. (2016). CAESAR: a new tool to assess relatives' experience of dying and death in the ICU. *Intensive Care Medicine*, *42*(6), 995–1002. https://doi /10.1007/s00134-016-4260-4

Khoudri, I., Ali Zeggwagh, A., Abidi, K., Madani, N., & Abouqal, R. (2007). Measurement properties of the short form 36 and health-related quality of life after intensive care in Morocco. *Acta anaesthesiologica Scandinavica*, *51*(2), 189–197. https://doi.org/10.1111/j.1399-6576.2006.01225.x

Khoudri, I., Belayachi, J., Dendane, T., Abidi, K., Madani, N., Zekraoui, A., Zeggwagh, A. A., & Abouqal, R. (2012). Measuring quality of life after intensive care using the Arabic version

for Morocco of the EuroQol 5 Dimensions. *BMC research notes*, *5*, 56. https://doi.org/10.1186/1756-0500-5-56

Lasiter, S., Oles, S. K., Mundell, J., London, S., & Khan, B. (2016). Critical Care Follow-up Clinics: A Scoping Review of Interventions and Outcomes. *Clinical Nurse Specialist CNS*, *30*(4), 227–237. https://doi.org/10.1097/NUR.0000000000000219

Levac, D., Colquhoun, H., & O'Brien, K. K. (2010). Scoping studies: advancing the methodology. *Implementation Science: IS*, *5*, 69. https://doi.org/10.1186/1748-5908-5-69

Lucas, N. P., Macaskill, P., Irwig, L., & Bogduk, N. (2010). The development of a quality appraisal tool for studies of diagnostic reliability (QAREL). *Journal of Clinical Epidemiology*, *63*(8), 854–861. https://doi.org/10.1016/j.jclinepi.2009.10.002.

McIlroy, P. A., King, R. S., Garrouste-Orgeas, M., Tabah, A., & Ramanan, M. (2019). The Effect of ICU Diaries on Psychological Outcomes and Quality of Life of Survivors of Critical Illness and Their Relatives: A Systematic Review and Meta-Analysis. *Critical Care Medicine*, *47*(2), 273–279. https://doi.org/10.1097/CCM.0000000000003547

Mikkelsen, M. E., Still, M., Anderson, B. J., Bienvenu, O. J., Brodsky, M. B., Brummel, N., Butcher, B., Clay, A. S., Felt, H., Ferrante, L. E., Haines, K. J., Harhay, M. O., Hope, A. A., Hopkins, R. O., Hosey, M., Hough, C. "Terri" L., Jackson, J. C., Johnson, A., Khan, B., … Sevin, C. M. (2020). Society of Critical Care Medicine's International Consensus Conference on Prediction and Identification of Long-Term Impairments After Critical Illness. *Critical Care Medicine*. https://doi.org/10.1097/CCM.0000000000004586

Milton, A., Brück, E., Schandl, A., Bottai, M., & Sackey, P. (2017). Early psychological screening of intensive care unit survivors: a prospective cohort study. *Critical care (London, England)*, *21*(1), 273. https://doi.org/10.1186/s13054-017-1813-z

Milton, A., Schandl, A., Soliman, I. W., Meijers, K., van den Boogaard, M., Larsson, I. M., Brorsson, C., Östberg, U., Oxenbøll-Collet, M., Savilampi, J., Paskins, S., Bottai, M., & Sackey, P. V. (2018). Development of an ICU discharge instrument predicting psychological morbidity: a multinational study. *Intensive care medicine*, *44*(12), 2038–2047. https://doi.org/10.1007/s00134-018-5467-3

Milton, A., Schandl, A., Soliman, I., Joelsson-Alm, E., van den Boogaard, M., Wallin, E., Brorsson, C., Östberg, U., Latocha, K., Savilampi, J., Paskins, S., Bottai, M., & Sackey, P. (2020). ICU discharge screening for prediction of new-onset physical disability-A multinational cohort study. *Acta anaesthesiologica Scandinavica*, *64*(6), 789–797. https://doi.org/10.1111/aas.13563

Needham, D. M., Davidson, J., Cohen, H., Hopkins, R. O., Weinert, C., Wunsch, H., Zawistowski, C., Bemis-Dougherty, A., Berney, S. C., Bienvenu, O. J., Brady, S. L., Brodsky, M. B., Denehy, L., Elliott, D., Flatley, C., Harabin, A. L., Jones, C., Louis, D., Meltzer, W., … Harvey, M. A. (2012). Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Critical Care Medicine*, *40*(2), 502–509. https://doi.org/10.1097/CCM.0b013e318232da75

Nickel, M., Nickel, C., Mitterlehner, F., Rother, W., Leiberich, P., Tritt, K., & Loew, T.. (n.d.). The occurrence of posttraumatic stress disorder in patients following intensive care treatment: A cross-sectional study in a random sample. *Journal of Intensive Care Medicine*, *19*(5), 285–290. https://doi /10.1177/0885066604267684

Oeyen, S. G., Vandijck, D. M., Benoit, D. D., Annemans, L., & Decruyenaere, J. M. (2010). Quality of life after intensive care: a systematic review of the literature. *Critical Care Medicine*, *38*(12), 2386–2400. https://doi.org/10.1097/CCM.0b013e3181f3dec5

Parker, A. M., Sricharoenchai, T., Raparla, S., Schneck, K. W., Bienvenu, O. J., & Needham, D. M. (2015). Posttraumatic stress disorder in critical illness survivors: a metaanalysis. *Critical Care Medicine*, *43*(5), 1121–1129. https://doi.org/10.1097/CCM.0000000000000882

Parsons, E. C., Palen, B., Hough, C. L., Vitiello, M. V., Zatzick, D., & Davydow, D. S.. (n.d.). Validity of a single PTSD checklist item to screen for insomnia in survivors of critical illness. *Heart and Lung*, *47*(2), 87–92. https://doi /10.1016/j.hrtlng.2017.12.006

Patrick, D. L., Danis, M., Southerland, L. I., & Hong, G. (1988). Quality of life following intensive care. *Journal of general internal medicine*, *3*(3), 218–223. https://doi.org/10.1007/BF02596335

Pfoh, E. R., Chan, K. S., Dinglas, V. D., Girard, T. D., Jackson, J. C., Morris, P. E., Hough, C. L., Mendez-Tellez, P. A., Ely, E. W., Huang, M., Needham, D. M., Hopkins, R. O., & NIH NHLBI ARDS Network (2015). Cognitive screening among acute respiratory failure survivors: a cross-sectional evaluation of the Mini-Mental State Examination. *Critical care (London, England)*, *19*(1), 220. https://doi.org/10.1186/s13054-015-0934-5

Pun, B. T., Balas, M. C., Barnes-Daly, M. A., Thompson, J. L., Aldrich, J. M., Barr, J., Byrum, D., Carson, S. S., Devlin, J. W., Engel, H. J., Esbrook, C. L., Hargett, K. D., Harmon, L., Hielsberg, C., Jackson, J. C., Kelly, T. L., Kumar, V., Millner, L., Morse, A., Perme, C. S., … Ely, E. W. (2019). Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults. *Critical care medicine*, *47*(1), 3–14. https://doi.org/10.1097/CCM.0000000000003482

Rabiee, A., Nikayin, S., Hashem, M. D., Huang, M., Dinglas, V. D., Bienvenu, O. J., ... & Needham, D. M. (2016). Depressive symptoms after critical illness: a systematic review

and meta-analysis. *Critical Care Medicine*, *44*(9), 1744-1753. https://doi:10.1097/CCM.0000000000001811

Rawal, G., Yadav, S., & Kumar, R. (2017). Post-intensive Care Syndrome: an Overview. *Journal of Translational Internal Medicine*, *5*(2), 90–92. https://doi.org/10.1515/jtim-2016-0016

Righy, C., Rosa, R. G., da Silva, R., Kochhann, R., Migliavaca, C. B., Robinson, C. C., Teche, S. P., Teixeira, C., Bozza, F. A., & Falavigna, M. (2019). Prevalence of post-traumatic stress disorder symptoms in adult critical care survivors: a systematic review and meta-analysis. *Critical care (London, England)*, *23*(1), 213. https://doi.org/10.1186/s13054-019-2489-3

Rosendahl, J., Kisyova, H., Gawlytta, R., & Scherag, A.. (n.d.). Comparative validation of three screening instruments for posttraumatic stress disorder after intensive care. *Journal of Critical Care*, *53*, 149–154. https://doi /10.1016/j.jcrc.2019.06.016

Rousseau, A. F., Prescott, H. C., Brett, S. J., Weiss, B., Azoulay, E., Creteur, J., Latronico, N., Hough, C. L., Weber-Carstens, S., Vincent, J. L., & Preiser, J. C. (2021). Long-term outcomes after critical illness: recent insights. *Critical care (London, England)*, *25*(1), 108. https://doi.org/10.1186/s13054-021-03535-3

Rousseau, A. F., Prescott, H. C., Brett, S. J., Weiss, B., Azoulay, E., Creteur, J., Latronico, N., Hough, C. L., Weber-Carstens, S., Vincent, J. L., & Preiser, J. C. (2021). Long-term outcomes after critical illness: recent insights. *Critical care (London, England)*, *25*(1), 108. https://doi.org/10.1186/s13054-021-03535-3

Schandl, A., Bottai, M., Hellgren, E., Sundin, O., & Sackey, P. V. (2013). Developing an early screening instrument for predicting psychological morbidity after critical illness. *Critical care (London, England)*, *17*(5), R210. https://doi.org/10.1186/cc13018

Schandl, A., Bottai, M., Holdar, U., Hellgren, E., & Sackey, P. (2014). Early prediction of new-onset physical disability after intensive care unit stay: a preliminary instrument. *Critical care (London, England)*, *18*(4), 455. https://doi.org/10.1186/s13054-014-0455-7

Scragg, P., Jones, A., & Fauvel, N. (2001). Psychological problems following ICU treatment*. *Anaesthesia*, *56*(1), 9–14.

Silveira, L., Silva, J., Soler, J., Sun, C., Tanaka, C., & Fu, C. (2018). Assessing functional status after intensive care unit stay: the Barthel Index and the Katz Index. *International journal for quality in health care : journal of the International Society for Quality in Health Care*, *30*(4), 265–270. https://doi.org/10.1093/intqhc/mzx203

Spies, C. D., Krampe, H., Paul, N., Denke, C., Kiselev, J., Piper, S. K., Kruppa, J., Grunow, J. J., Steinecke, K., Gülmez, T., Scholtz, K., Rosseau, S., Hartog, C., Busse, R., Caumanns, J., Marschall, U., Gersch, M., Apfelbacher, C., Weber-Carstens, S., & Weiss, B. (2021). Instruments to measure outcomes of post-intensive care syndrome in outpatient care settings - Results of an expert consensus and feasibility field test. *Journal of the Intensive Care Society*, *22*(2), 159–174. https://doi.org/10.1177/1751143720923597

Stoll, C., Kapfhammer, H. P., Rothenhäusler, H. B., Haller, M., Briegel, J., Schmidt, M., Krauseneck, T., Durst, K., & Schelling, G. (1999). Sensitivity and specificity of a screening test to document traumatic experiences and to diagnose post-traumatic stress disorder in ARDS patients after intensive care treatment. *Intensive Care Medicine*, *25*(7), 697–704. https://doi /10.1007/s001340050932

Sukantarat, K. T., Williamson, R. C., & Brett, S. J. (2007). Psychological assessment of ICU survivors: a comparison between the Hospital Anxiety and Depression scale and the

Depression, Anxiety and Stress scale. *Anaesthesia*, *62*(3), 239–243. https://doi.org/10.1111/j.1365-2044.2006.04948.x

Tian, Z. M., & Reis Miranda, D. (1995). Quality of life after intensive care with the sickness impact profile. *Intensive Care Medicine*, *21*(5), 422–428. https://doi /10.1007/bf01707411

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., Lewin, S., … Straus, S. E. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of internal medicine*, *169*(7), 467–473. https://doi.org/10.7326/M18-0850

Twigg, E., Humphris, G., Jones, C., Bramwell, R., & Griffiths, R. D. (2008). Use of a screening questionnaire for post-traumatic stress disorder (PTSD) on a sample of UK ICU patients. *Acta anaesthesiologica Scandinavica*, *52*(2), 202–208. https://doi.org/10.1111/j.1399-6576.2007.01531.x

Umberger R. (2019). What is the best core measure after critical illness when the IES-R is no longer accessible for new researchers?. *Critical care (London, England)*, *23*(1), 313. https://doi.org/10.1186/s13054-019-2595-2

Wade, D. F., Moon, Z., Windgassen, S. S., Harrison, A. M., Morris, L., & Weinman, J. A. (2016). Non-pharmacological interventions to reduce ICU-related psychological distress: a systematic review. *Minerva Anestesiologica*, *82*(4), 465–478.

Wang, S., Allen, D., Perkins, A., Monahan, P., Khan, S., Lasiter, S., Boustani, M., & Khan, B. (2019). Validation of a New Clinical Tool for Post-Intensive Care Syndrome. *American*

journal of critical care: an official publication, American Association of Critical-Care Nurses, *28*(1), 10–18. https://doi.org/10.4037/ajcc2019639

Warlan, H. (2016). Detection of Posttraumatic Stress Symptoms in Patients After Discharge from Intensive Care. *American Journal of Critical Care*, *25*(6), 509–515. https://doi /10.4037/ajcc2016573

Wassenaar, A., de Reus, J., Donders, A., Schoonhoven, L., Cremer, O. L., de Lange, D. W., van Dijk, D., Slooter, A., Pickkers, P., & van den Boogaard, M. (2018). Development and Validation of an Abbreviated Questionnaire to Easily Measure Cognitive Failure in ICU Survivors: A Multicenter Study. *Critical care medicine*, *46*(1), 79–84. https://doi.org/10.1097/CCM.0000000000002806

Wintermann, G. B., Rosendahl, J., Weidner, K., Strauß, B., Hinz, A., & Petrowski, K. (2018). Fatigue in chronically critically ill patients following intensive care - reliability and validity of the multidimensional fatigue inventory (MFI-20). *Health and quality of life outcomes*, *16*(1), 37. https://doi.org/10.1186/s12955-018-0862-6

Yuan, C., Timmins, F., & Thompson, D. R. (2021). Post-intensive care syndrome: A concept analysis. *International Journal of nursing studies*, *114*, 103814. https://doi.org/10.1016/j.ijnurstu.2020.103814

Zante, B., Camenisch, S. A., & Schefold, J. C. (2020). Interventions in Post-Intensive Care Syndrome-Family: A Systematic Literature Review. *Critical care medicine*, *48*(9), e835–e840. https://doi.org/10.1097/CCM.0000000000004450

Conclusion

PICS is a major long-term complication of critical illness for both patients and their families causing significant loss of function and worsening quality of life. Early detection and treatment of such morbidities is required to minimize long-term sequelae, reduce the rate of re-hospitalization, and optimize functional recovery. Recognizing the lack of a unified approach for PICS and PTSD after ICU discharge, in this thesis, I critically reviewed evidence on the effects of music on the brain, especially in relation to PTSD symptoms. Moreover, since the first step in the management of PICS/PTSD is reliable assessment, I reviewed the scope, characteristics and metric properties of current tools for the assessment of PICS/PTSD post-ICU. This review of tools provided insights that can inform selection of a tool for specific ICU populations and their families and development of future tools. I identified only five tools addressing all 3 domains of PICS, while the validity and feasibility of the tools is unclear, especially for 2-4 weeks post-discharge. Only the tools addressing mental health appear to have appropriate psychometric properties and feasibility, whereas the diagnostic accuracy of cognitive assessment tools is limited. Only 2 tools, PICSQ and RAIN, address PICS in families, with appropriate psychometric properties. RAIN demonstrated high floor/ceiling effect (48.1%) and hence needs further evaluations for the diagnostic accuracy in ICU survivors (Bergbom et al., 2018). However, PICSQ revealed good sensitivity and specificity in survivors from a comprehensive ICU population such as cardiac, neurological, trauma, gastrointestinal, respiratory, and renal inclusive of both planned and unplanned admissions (Jeong & Kang, 2019; Kang et al., 2020). Most importantly PICSQ includes expert recommended PICS symptom to measure physical, psychological, and cognitive impairment (Needham et al., 2017). Using the PICSQ instead of different tools for each domain of PICS in the post-ICU clinics will increase the effectiveness of screenings, evaluations of

interventions, and follow-up management. Specifically, nurses can easily screen ICU survivors at risk of PICS and help provide timely interventions as needed. In addition, PICSQ can be used in research work to evaluate various interventions provided for PICS prevention or reduction. However, the study was only conducted in Korea, and, hence, may have limited generalizability. Therefore, more studies in diverse settings are needed for comprehensive validation of PICSQ to screen PICS in ICU survivors.

PTSD is part of the post-ICU syndrome and impairs the quality of life and functionality of increasing numbers of ICU survivors and their families worldwide. Through a critical review, I demonstrated key brain structures in PTSD symptomatology and the effect of music and sound on these structures.

Music can target the key brain areas involved in PTSD symptomatology, as shown diagrammatically in Figure 1. These results establish the possibility of music as a cost-effective, easy to access intervention to purposefully address post-ICU PTSD and improve the quality of life of both the ICU survivors and their families. Results from the existing experimental studies among PTSD patients shows that music can effectively:

a) improve coping,

b) improve emotional regulation,

c) decrease depression,

d) decrease anxiety levels,

e) decrease dissociation symptoms,

f) decrease overall severity of PTSD, and

g) improve quality of life.

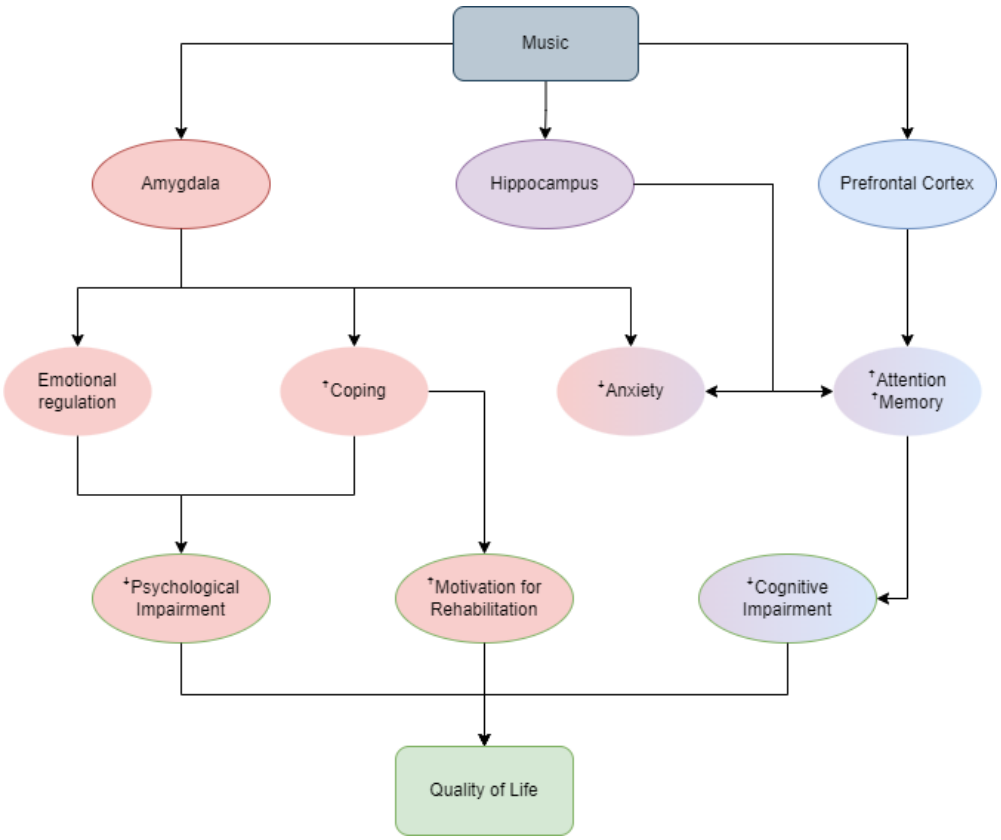

Figure 1. Potential effect of music in post-ICU symptomatology

A number of research hypotheses for the management of PICS can be derived from those effects. For example, due to music effects on the hippocampus and memory we can hypothesize that music interventions would be beneficial for cognitive impairments port-ICU. Indeed, several studies show the impact of music in cognitive outcomes in individuals with dementia and elderly individuals (Gonzalez et al., 2021; Moreno-Morales et al., 2020; Stapleton, 2020). A study by González-Ojea et al., 2021 demonstrated physical activity along with music therapy can be used as a non-invasive preventive pharmacological treatment to improve memory, and reduce frailty in institutionalized elderly people with dementia. Furthermore, a meta-analysis of eight interventional studies with 816 subjects assessing effectiveness of music in dementia patients, showed that music interventions significantly improve cognitive function in people living with

dementia, as well as quality of life after the intervention (Moreno-Morales et al., 2020). Similarly, there is evidence that music-based interventions can also improve verbal memory and focused attention in stroke patients (Moumdjian et al., 2017). Moreover, music has shown to facilitate functional rehabilitation in several populations although it has not been tested in ICU survivors. Catherine et al., 2021 incorporated therapeutic instrumental music to entertain movement in stroke rehabilitation program and found significant effects of music in improving upper extremity impairment in just 9 intervention sessions. Moreover, a systematic review of 11 studies with 290 participants suggested that active music therapy can be incorporated as a potential adjunctive to physical rehabilitation to improve motor skills (Kogutek et al., 2016). Another systematic review of 19 studies found that instrument-based music interventions can improve fine motor dexterity and gross motor functions in stroke patients (Moumdjian et al., 2017). Also, there is evidence that adding music to the functional rehabilitation reduces the dropout rates of the rehabilitation programs (Hackney et al., 2015).

Insights into the therapeutic potential of music by determining which types of music are best suited to stimulate specific limbic brain structures can lead to a more systematic use of music in the therapy of PTSD. From the literature it was evident that basic psychoacoustic properties of music, such as pitch (high or low tone of sounds), rate (fast or slow speed of sounds), loudness (loud or soft intensity of sounds), mode (major or minor key), timbre, and rhythm are the key factors to consider. The review demonstrated that music with slower tempo, low pitch, containing primarily string composition, regular rhythmic patterns, no extreme changes in dynamics, and no lyrics can induce relaxation and emotional regulation in PTSD patients. Moreover, predictable music can be used to initiate positive responses such as reward, appraisal, and pleasantness which is vital in PTSD symptomatology. The findings also emphasised on the importance of participant-

selected music and continuous therapist involvement to enhance effectiveness of music interventions and participant retention.

Altogether, this study provides a framework for the assessment and management of PTSD in ICU survivors through music interventions. The findings of this research can inform nurses, clinicians, researchers, as well as policy makers about the best way to assess and manage these complications. Initial assessment with brief screening tools can help identify the individuals with or at risk of PTSD/PICS. Since brief screening tools are easy to use and do not require extensive training, they could be incorporated into patient follow-up after discharge from the ICU. This could be the initial stage in the diagnosis and treatment of PTSD/PICS followed by a final intensive diagnosis by a specialist. Moreover, this could possibly decrease the burden and overcrowding of specialist clinics making them more accessible for the ones in need. Further, following a final confirming diagnosis by the specialist, PICS/PTSD patients could then be referred to initiate treatment at an early stage. Another important contribution of this research is the groundwork for music and sound interventions to treat PTSD in ICU survivors. The neurobiology of PTSD symptomatology and the possible mechanism of music presented through this research could be useful for future studies to consider music as a nonpharmacological treatment option for ICU survivors. Moreover, this research also highlights important considerations for maximizing the impact of targeted music interventions in post-ICU survivors such as duration of sessions, repetition, length of intervention, and specific patient populations. Thus, this research contributes to improving patients' mental states and developing strategies for early assessment and management. Most importantly it provides important considerations for future research in the development of assessment tools and investigation of music as a potential approach to managing PTSD in ICU survivors.

Reference

Bergbom, I., Karlsson, V., & Ringdal, M. (2018). Developing and evaluating an instrument to measure Recovery After INtensive care: the RAIN instrument. *BMC nursing*, *17*, 5. https://doi.org/10.1186/s12912-018-0275-1

Catherine M. Haire, P., Luc Tremblay, P., Veronica Vuong, M., Kara K. Patterson, P., Joyce L. Chen, P., Jonathan H. Burdette, M., Nina Schaffert, P., & Michael H. Thaut, P. (2021). Therapeutic Instrumental Music Training and Motor Imagery in Post-Stroke Upper-Extremity Rehabilitation: A Randomized-Controlled Pilot Study. *Archives of Rehabilitation Research and Clinical Translation*, *3*(4). https://doi.org/10.1016/j.arrct.2021.100162

Gonzalez-Ojea, M. J., Dominguez-Lloria, S., Portela-Pino, I., & Alvarinas-Villaverde, M. (2021). Physical and Cognitive Functioning of Institutionalized Elderly People in Rural Areas. Preventive Actions Using Physical Activity and Music Therapy. *HEALTHCARE*, *9*(11), 1536. https://doi.org/10.3390/healthcare9111536

Hackney, M. E., & Bennett, C. G. (2014). Dance therapy for individuals with Parkinson's disease: improving quality of life. *Research and Reviews in Parkinsonism*, *4*, 17-25.

Jeong, Y. J., & Kang, J.. (2019). Development and validation of a questionnaire to measure post-intensive care syndrome. *Intensive and Critical Care Nursing*, *55*. https://doi /10.1016/j.iccn.2019.102756

Kang, J., Jeong, Y. J., & Hong, J. (2020). Cut-Off Values of the Post-Intensive Care Syndrome Questionnaire for the Screening of Unplanned Hospital Readmission within One Year. *Journal of Korean Academy of Nursing*, *50*(6), 787–798. https://doi.org/10.4040/jkan.20233

Kogutek, D. L., Holmes, J. D., Grahn, J. A., Lutz, S. G., & Ready, E. (2016). Active Music Therapy and Physical Improvements From Rehabilitation for Neurological Conditions. *Advances in mind-body medicine*, *30*(4), 14–22.

Moreno-Morales, C., Calero, R., Moreno-Morales, P., & Pintado, C. (2020). Music Therapy in the Treatment of Dementia: A Systematic Review and Meta-Analysis. *Frontiers in medicine*, *7*, 160. https://doi.org/10.3389/fmed.2020.00160

Moumdjian, L., Sarkamo, T., Leone, C., Leman, M., & Feys, P. (2017). Effectiveness of music-based interventions on motricity or cognitive functioning in neurological populations: a systematic review. *European journal of physical and rehabilitation medicine*, *53*(3), 466–482. https://doi.org/10.23736/S1973-9087.16.04429-4

Needham, D. M., Sepulveda, K. A., Dinglas, V. D., Chessare, C. M., Friedman, L. A., Bingham, C. O., 3rd, & Turnbull, A. E. (2017). Core Outcome Measures for Clinical Research in Acute Respiratory Failure Survivors. An International Modified Delphi Consensus Study. *American journal of respiratory and critical care medicine*, *196*(9), 1122–1130. https://doi.org/10.1164/rccm.201702-0372OC

Stapleton, K. (2020). Music and Dementia: From Cognition to Therapy. *Journal of Sociology & Social Welfare*, *47*(3), 219–222.

Bibliography

Akerman, E., Fridlund, B., Ersson, A., & Granberg-Axéll, A. (2009). Development of the 3-SET 4P questionnaire for evaluating former ICU patients' physical and psychosocial problems over time: a pilot study. *Intensive & critical care nursing*, *25*(2), 80–89. https://doi.org/10.1016/j.iccn.2008.06.004

Akerman, E., Fridlund, B., Samuelson, K., Baigi, A., & Ersson, A. (2013). Psychometric evaluation of 3-set 4P questionnaire. *Intensive & critical care nursing*, *29*(1), 40–47. https://doi.org/10.1016/j.iccn.2012.06.002

Amass, T. H., Villa, G., OMahony, S., Badger, J. M., McFadden, R., Walsh, T., Caine, T., McGuirl, D., Palmisciano, A., Yeow, M. E., De Gaudio, R., Curtis, J. R., & Levy, M. M. (2020). Family Care Rituals in the ICU to Reduce Symptoms of Post-Traumatic Stress Disorder in Family Members-A Multicenter, Multinational, Before-and-After Intervention Trial. *Critical Care Medicine*, *48*(2), 176–184. https://doi.org/10.1097/CCM.0000000000004113

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

American Psychological Association. (2017). Clinical practice guideline for the treatment of posttraumatic stress disorder (PTSD) in adults. Retrieved from: *https://www.apa.org/ptsd-guideline*

Amra, S., John C., O., Mikhail, D., Dziadzko, V., Rashid, A., Tarun D., S., Rahul, K., Ann M., F., John D., F., Ronald, P., Ognjen, G., & Alejandro A., R. (2018). Potentially Modifiable Risk Factors for Long-Term Cognitive Impairment After Critical Illness: A Systematic Review. *Mayo Clinic Proceedings*, *93*(1), 68–82.

Anand, K. S., & Dhikav, V. (2012) Hippocampus in health and disease: An overview. Annals of Indian Academy of Neurology, 15(4), 239–246. https://doi.org/10.4103/0972-2327.104323

Annachiara, M., Pratik P., P., Timothy D., G., Mayur B., P., Christopher G., H., James C., J., Jennifer L., T., Rameela, C., Eugene Wesley, E., & Nathan E., B. (2018). Co-Occurrence of Post-Intensive Care Syndrome Problems Among 406 Survivors of Critical Illness*. *Critical Care Medicine*, *46*(9), 1393–1401. https://doiorg.login.ezproxy.library.ualberta.ca/10.1097/CCM.0000000000003218

Appleton, R. T., Kinsella, J., & Quasim, T. (2015). The incidence of intensive care unit-acquired weakness syndromes: A systematic review. *Journal of the Intensive Care Society*, *16*(2), 126–136. https://doi.org/10.1177/1751143714563016

Armony, J. L., Aubé, W., Angulo-Perkins, A., Peretz, I., & Concha, L. (2015) The specificity of neural responses to music and their relation to voice processing: an fMRI-adaptation study. Neuroscience letters, 593, 35–39. https://doi.org/10.1016/j.neulet.2015.03.011

Arnsten A. F. (2009) Stress signalling pathways that impair prefrontal cortex structure and function. Nature Reviews. Neuroscience, 10(6), 410–422. https://doi.org/10.1038/nrn2648

Astill Wright, L., Sijbrandij, M., Sinnerton, R., Lewis, C., Roberts, N. P., & Bisson, J. I. (2019). Pharmacological prevention and early treatment of post-traumatic stress disorder and acute stress disorder: a systematic review and meta-analysis. *Translational psychiatry*, *9*(1), 334. https://doi.org/10.1038/s41398-019-0673-5

Baethge, C., Goldbeck-Wood, S., & Mertens, S. (2019) SANRA-a scale for the quality assessment of narrative review articles. Research integrity and peer review, 4, 5. https://doi.org/10.1186/s41073-019-0064-8

Baker, F. A., Metcalf, O., Varker, T., & O'Donnell, M. (2018) A systematic review of the efficacy of creative arts therapies in the treatment of adults with PTSD. Psychological Trauma: Theory, Research, Practice and Policy, 10(6), 643–651. https://doi.org/10.1037/tra0000353

Bastian, K., Hollinger, A., Mebazaa, A., Azoulay, E., Féliot, E., Chevreul, K., Fournier, M. C., Guidet, B., Michel, M., Montravers, P., Pili-Floury, S., Sonneville, R., Siegemund, M., Gayat, E., & FROG-ICU Study Investigators (2018). Association of social deprivation with 1-year outcome of ICU survivors: results from the FROG-ICU study. *Intensive care medicine*, *44*(12), 2025–2037. https://doi.org/10.1007/s00134-018-5412-5

Baumbach, P., Götz, T., Meissner, W., Guenther, A., & Witte, O. W. . (n.d.). Perceived cognitive impairments after critical illness: a longitudinal study in survivors and family member controls. *Acta Anaesthesiologica Scandinavica*, *60*(8), 1121–1130. https://doi /10.1111/aas.12755

Beck, B. D., Messel, C., Meyer, S. L., Cordtz, T. O., Søgaard, U., Simonsen, E., & Moe, T. (2017) Feasibility of trauma-focused Guided Imagery and Music with adult refugees diagnosed with PTSD: A pilot study. Nordic Journal of Music Therapy, 1–20. https://doi.org/10.1080/08098131.2017.1286368

Beck, B. D., Meyer, S. L., Simonsen, E., Søgaard, U., Petersen, I., Arnfred, S., Tellier, T., & Moe, T. (2021) Music therapy was noninferior to verbal standard treatment of traumatized refugees in mental health care: Results from a randomized clinical trial. European Journal of Psychotraumatology, 12(1), 1930960. https://doi.org/10.1080/20008198.2021.1930960

Bensimon, M., Amir, D., & Wolf, Y. (2008) Drumming through trauma: Music therapy with post-traumatic soldiers. The Arts in Psychotherapy, 35(1), 34–48. https://doi.org/10.1016/j.aip.2007.09.002

Bergbom, I., Karlsson, V., & Ringdal, M. (2018). Developing and evaluating an instrument to measure Recovery After INtensive care: the RAIN instrument. *BMC nursing*, *17*, 5. https://doi.org/10.1186/s12912-018-0275-1

Bienvenu, J. O., Williams, J. B., Yang, A., Hopkins, R. O., & Needham, D. M. (2013). Posttraumatic Stress Disorder in Survivors of Acute Lung Injury: Evaluating the Impact of Event Scale-Revised. *Chest*, *144*(1), 24–31. https://doi /10.1378/chest.12-0908

Blanaru, M., Bloch, B., Vadas, L., Arnon, Z., Ziv, N., Kremer, I., & Haimov, I. (2012). The effects of music relaxation and muscle relaxation techniques on sleep quality and emotional measures among individuals with posttraumatic stress disorder. *Mental Illness*, *4*(2), e13. https://doi.org/10.4081/mi.2012.e13

Boccia, M., D'Amico, S., Bianchini, F., Marano, A., Giannini, A. M., & Piccardi, L. (2016) Different neural modifications underpin PTSD after different traumatic events: an fMRI meta-analytic study. Brain imaging and behavior, 10(1), 226–237. https://doi.org/10.1007/s11682-015-9387-3

Bohart, S., Egerod, I., Bestle, M. H., Overgaard, D., Christensen, D. F., & Jensen, J. F. (2018). Recovery programme for ICU survivors has no effect on relatives' quality of life: Secondary analysis of the RAPIT-study. *Intensive & critical care nursing*, *47*, 39–45. https://doi.org/10.1016/j.iccn.2018.03.002

Bradt, J., & Dileo, C. (2014) Music interventions for mechanically ventilated patients. *The Cochrane database of systematic reviews*, *2014*(12), CD006902. https://doi.org/10.1002/14651858.CD006902

Bradt, J., Dileo, C., & Shim, M. (2013) Music interventions for preoperative anxiety. The Cochrane Database of Systematic Reviews, (6), CD006908. https://doi.org/10.1002/14651858.CD006908

Briegel, I., Dolch, M., Irlbeck, M., Hauer, D., Kaufmann, I., & Schelling, G. (2013). Ergebnisqualität der Therapie des akuten Lungenversagens : Veränderungen über einen Zeitraum von 2 Jahrzehnten [Quality of results of therapy of acute respiratory failure : changes over a period of two decades]. *Der Anaesthesist*, *62*(4), 261–270. https://doi.org/10.1007/s00101-013-2156-z

Brown, S. M., Collingridge, D. S., Wilson, E. L., Beesley, S., Bose, S., Orme, J., Jackson, J., & Hopkins, R. O. (2018). Preliminary Validation of the Montreal Cognitive Assessment Tool among Sepsis Survivors: A Prospective Pilot Study. *Annals of the American Thoracic Society*, *15*(9), 1108–1110. https://doi.org/10.1513/AnnalsATS.201804-233OC

Bruscia, K. E. Defining music therapy (2nd ed.). Barcelona Publishers (1998).

Canadian Association of Music Therapists (2020). About music therapy. Available online: https://www.musictherapy.ca/about-camt-music-therapy/about-music-therapy/ (accessed on 13 November 2021)

Cantor, P. (2021). The Stress of This Moment Might Be Hurting Kids' Development. Available online: https://turnaroundusa.org/pamela-cantor-m-d-pens-guest-post-for-education-next/ (accessed on 13 November 2021)

Carr, C., d'Ardenne, P., Sloboda, A., Scott, C., Wang, D., & Priebe, S. (2012). Group music therapy for patients with persistent post-traumatic stress disorder--an exploratory randomized controlled trial with mixed methods evaluation. *Psychology and Psychotherapy*, *85*(2), 179–202. https://doi.org/10.1111/j.2044-8341.2011.02026.x

Catherine M. Haire, P., Luc Tremblay, P., Veronica Vuong, M., Kara K. Patterson, P., Joyce L. Chen, P., Jonathan H. Burdette, M., Nina Schaffert, P., & Michael H. Thaut, P. (2021). Therapeutic Instrumental Music Training and Motor Imagery in Post-Stroke Upper-Extremity Rehabilitation: A Randomized-Controlled Pilot Study. *Archives of Rehabilitation Research and Clinical Translation*, *3*(4). https://doi.org/10.1016/j.arrct.2021.100162

Chan, K. S., Pfoh, E. R., Denehy, L., Elliott, D., Holland, A. E., Dinglas, V. D., & Needham, D. M. (2015). Construct validity and minimal important difference of 6-minute walk distance in survivors of acute respiratory failure. *Chest*, *147*(5), 1316–1326. https://doi.org/10.1378/chest.14-1808

Chariyawong, P., Copeland, S., & Mulkey, Z. (2016). What is the role of music in the intensive care unit?. *The Southwest Respiratory and Critical Care Chronicles*, *4*(16), 40-44.

Chetty, S., Friedman, A. R., Taravosh-Lahn, K., Kirby, E. D., Mirescu, C., Guo, F., Krupik, D., Nicholas, A., Geraghty, A., Krishnamurthy, A., Tsai, M. K., Covarrubias, D., Wong, A., Francis, D., Sapolsky, R. M., Palmer, T. D., Pleasure, D., & Kaufer, D. (2014) Stress and glucocorticoids promote oligodendrogenesis in the adult hippocampus. Molecular Psychiatry, 19(12), 1275–1283. https://doi.org/10.1038/mp.2013.190.

Chlan, L. L., Heiderscheit, A., Skaar, D. J., & Neidecker, M. V. (2018) Economic Evaluation of a Patient-Directed Music Intervention for ICU Patients Receiving Mechanical Ventilatory Support. Critical Care Medicine, 46(9), 1430–1435. https://doi.org/10.1097/CCM.0000000000003199

Choi, J., Donahoe, MP., Hoffman, L.A., (2016). Psychological and physical health in family caregivers of intensive care unit survivors: current knowledge and future research

strategies. *Journal of Korean Academy of Nursing*;46(2):159-167. http://dx.doi.org/10.4040/jkan.2016.46.2.159

Chrispin, P. S., Scotton, H., Rogers, J., Lloyd, D., & Ridley, S. A. (1997). Short Form 36 in the intensive care unit: assessment of acceptability, reliability and validity of the questionnaire. *Anaesthesia*, *52*(1), 15–23.

Christie, J. D., Biester, R. C., Taichman, D. B., Shull, W. H., Jr, Hansen-Flaschen, J., Shea, J. A., & Hopkins, R. O. (2006). Formation and validation of a telephone battery to assess cognitive function in acute respiratory distress syndrome survivors. *Journal of critical care*, *21*(2), 125–132. https://doi.org/10.1016/j.jcrc.2005.11.004

Chu, B., Marwaha, K., Sanvictores, T., & Ayers, D. (2021). Physiology, Stress Reaction. In StatPearls. StatPearls Publishing. Available online: https://www.ncbi.nlm.nih.gov/books/NBK541120/ (accessed on 13 November 2021)

Chung, C. R., Yoo, H. J., Park, J., & Ryu, S. (2017). Cognitive Impairment and Psychological Distress at Discharge from Intensive Care Unit. *Psychiatry investigation*, *14*(3), 376–379. https://doi.org/10.4306/pi.2017.14.3.376

Coburn D. (2018) Using MR to View PTSD's Effect on the Amygdala and Hippocampus. Radiologic technology, 89(5), 501–504.

Colbenson, G. A., Johnson, A., & Wilson, M. E. (2019). Post-intensive care syndrome: impact, prevention, and management. *Breathe (Sheffield, England)*, *15*(2), 98–101. https://doi.org/10.1183/20734735.0013-2019

Collet, M. O., Egerod, I., Thomsen, T., Wetterslev, J., Lange, T., Ebdrup, B. H., & Perner, A. (2021). Risk factors for long-term cognitive impairment in ICU survivors: A multicenter,

prospective cohort study. *Acta anaesthesiologica Scandinavica*, *65*(1), 92–99. https://doi.org/10.1111/aas.13692

Colquhoun, H. L., Levac, D., O'Brien, K. K., Straus, S., Tricco, A. C., Perrier, L., Kastner, M. & Moher, D. (2014). Scoping reviews: time for clarity in definition, methods, and reporting. *Journal of Clinical Epidemiology, 67*(12), 1291-1294. doi:10.1016/j.jclinepi.2014.03.013

Corner, E. J., Soni, N., Handy, J. M., & Brett, S. J. (2014). Construct validity of the Chelsea critical care physical assessment tool: an observational study of recovery from critical illness. *Critical care (London, England)*, *18*(2), R55. https://doi.org/10.1186/cc13801

Corner, E. J., Wood, H., Englebretsen, C., Thomas, A., Grant, R. L., Nikoletou, D., & Soni, N. (2013). The Chelsea critical care physical assessment tool (CPAx): validation of an innovative new tool to measure physical morbidity in the general adult critical care population; an observational proof-of-concept pilot study. *Physiotherapy*, *99*(1), 33–41. https://doi.org/10.1016/j.physio.2012.01.003

Cox, C. E., Hough, C. L., Carson, S. S., White, D. B., Kahn, J. M., Olsen, M. K., Jones, D. M., Somers, T. J., Kelleher, S. A., & Porter, L. S. (2018). Effects of a Telephone- and Web-based Coping Skills Training Program Compared with an Education Program for Survivors of Critical Illness and Their Family Members. A Randomized Clinical Trial. *American Journal of Respiratory and Critical Care Medicine*, *197*(1), 66–78. https://doi.org/10.1164/rccm.201704-0720OC

Cukor, J., Olden, M., Lee, F., & Difede, J. (2010). Evidence-based treatments for PTSD, new directions, and special challenges. *Annals of the New York Academy of Sciences*, *1208*, 82–89. https://doi.org/10.1111/j.1749-6632.2010.05793.x

Davidson, J. E., Harvey, M. A., Schuller, J., & Black, G. (2013). Post-intensive care syndrome: What it is and how to help prevent it. *American Nurse Today*, *8*(5), 32-8.

Davidson, J. E., Jones, C., & Bienvenu, O. J. (2012). Family response to critical illness: postintensive care syndrome-family. *Critical Care Medicine*, *40*(2), 618–624. https://doi.org/10.1097/CCM.0b013e318236ebf9

Davydow, D. S., Desai, S. V., Needham, D. M., & Bienvenu, O. J. (2008) Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. Psychosomatic Medicine, 70(4), 512–519. https://doi.org/10.1097/PSY.0b013e31816aa0dd

Davydow, D. S., Gifford, J. M., Desai, S. V., Needham, D. M., & Bienvenu, O. J. (2008) Posttraumatic stress disorder in general intensive care unit survivors: a systematic review. General Hospital Psychiatry, 30(5), 421–434. https://doi.org/10.1016/j.genhosppsych.2008.05.006

Davydow, D. S., Zatzick, D., Hough, C. L., & Katon, W. J. (2013). In-hospital acute stress symptoms are associated with impairment in cognition 1 year after intensive care unit admission. *Annals of the American Thoracic Society*, *10*(5), 450–457. https://doi.org/10.1513/AnnalsATS.201303-060OC

Day, A., Haj-Bakri, S., Lubchansky, S., & Mehta, S. (2013). Sleep, anxiety and fatigue in family members of patients admitted to the intensive care unit: a questionnaire study. *Critical Care (London, England)*, *17*(3), R91. https://doi.org/10.1186/cc12736

de Witte, M., Spruit, A., van Hooren, S., Moonen, X., & Stams, G. J. (2020) Effects of music interventions on stress-related outcomes: a systematic review and two meta-analyses. Health Psychology Review, 14(2), 294–324. https://doi.org/10.1080/17437199.2019.1627897

Delgado, M. R., Nearing, K. I., Ledoux, J. E., & Phelps, E. A. (2008) Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. Neuron, 59(5), 829–838. https://doi.org/10.1016/j.neuron.2008.06.029

DellaVolpe, J. D., & Huang, D. T. (2015). Is there a role for music in the ICU? Critical Care (2016), 19. https://doi-org./10.1186/s13054-014-0663-1

Desai, R. (2019). Drug addiction. Available online: https://drrajivdesaimd.com/wp-content/uploads/2019/06/brain-and-drug-2.jpg (accessed on 13 November 2021).

Desai, S. V., Law, T. J., & Needham, D. M. (2011) Long-term complications of critical care. Critical Care Medicine 39(2), 371–379. https://doi.org/10.1097/CCM.0b013e3181fd66e5

Ding, Y., Zhang, Y., Zhou, W., Ling, Z., Huang, J., Hong, B., & Wang, X. (2019) Neural Correlates of Music Listening and Recall in the Human Brain. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 39(41), 8112–8123. https://doi.org/10.1523/JNEUROSCI.1468-18.2019

Dinglas, V. D., Aronson Friedman, L., Colantuoni, E., Mendez-Tellez, P. A., Shanholtz, C. B., Ciesla, N. D., Pronovost, P. J., & Needham, D. M. (2017). Muscle Weakness and 5-Year Survival in Acute Respiratory Distress Syndrome Survivors. *Critical care medicine*, *45*(3), 446–453. https://doi.org/10.1097/CCM.0000000000002208

Dunlop, B. W., & Wong, A. (2019) The hypothalamic-pituitary-adrenal axis in PTSD: Pathophysiology and treatment interventions. Progress in neuro-psychopharmacology & biological psychiatry, 89, 361–379. https://doi.org/10.1016/j.pnpbp.2018.10.010

Ehlert, U., Gaab, J., & Heinrichs, M. (2001) Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders:

the role of the hypothalamus-pituitary-adrenal axis. Biological Psychology, 57(1-3), 141–152. https://doi.org/10.1016/s0301-0511(01)00092-8

Estrup, S., Kjer, C., Vilhelmsen, F., Poulsen, L. M., Gøgenur, I., & Mathiesen, O. (2018). Cognitive Function 3 and 12 Months After ICU Discharge-A Prospective Cohort Study. *Critical care medicine*, *46*(12), e1121–e1127. https://doi.org/10.1097/CCM.0000000000003391

Etkin, A., & Wager, T. D. (2007) Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. The American journal of psychiatry, 164(10), 1476–1488. https://doi.org/10.1176/appi.ajp.2007.07030504

Ferrari, R. (2015) Writing narrative style literature reviews. Medical Writing, 24(4), 230-235. https://doi.org/10.1179/2047480615Z.000000000329

Finn, S., & Fancourt, D. (2018) The biological impact of listening to music in clinical and nonclinical settings: A systematic review. Progress in Brain Research, 237, 173–200. https://doi.org/10.1016/bs.pbr.2018.03.007

Flor, H., & Nees, F. (2014) Learning, memory, and brain plasticity in posttraumatic stress disorder: context matters. Restorative neurology and neuroscience, 32(1), 95–102. https://doi.org/10.3233/RNN-139013

Fuchs, E., & Flügge, G. (2014) Adult neuroplasticity: more than 40 years of research. Neural plasticity. Article 541870. https://doi.org/10.1155/2014/541870

Fuke, R., Hifumi, T., Kondo, Y., Hatakeyama, J., Takei, T., Yamakawa, K., Inoue, S., & Nishida, O. (2018). Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: a systematic review and meta-analysis. *BMJ open*, *8*(5), e019998. https://doi.org/10.1136/bmjopen-2017-019998

Fukui, H., & Toyoshima, K. (2008) Music facilitates the neurogenesis, regeneration, and repair of neurons. Medical hypotheses, 71(5), 765–769. https://doi.org/10.1016/j.mehy.2008.06.019

Garrouste-Orgeas, M., Flahault, C., Vinatier, I., Rigaud, J. P., Thieulot-Rolin, N., Mercier, E., Rouget, A., Grand, H., Lesieur, O., Tamion, F., Hamidfar, R., Renault, A., Parmentier-Decrucq, E., Monseau, Y., Argaud, L., Bretonnière, C., Lautrette, A., Badié, J., Boulet, E., Floccard, B., … Timsit, J. F. (2019). Effect of an ICU Diary on Posttraumatic Stress Disorder Symptoms Among Patients Receiving Mechanical Ventilation: A Randomized Clinical Trial. *JAMA*, *322*(3), 229–239. https://doi.org/10.1001/jama.2019.9058

Geense, W. W., Zegers, M., Peters, M., Ewalds, E., Simons, K. S., Vermeulen, H., van der Hoeven, J. G., & van den Boogaard, M. (2021). New Physical, Mental, and Cognitive Problems 1 Year after ICU Admission: A Prospective Multicenter Study. *American journal of respiratory and critical care medicine*, *203*(12), 1512–1521. https://doi.org/10.1164/rccm.202009-3381OC

Geretsegger, M., Elefant, C., Mössler, KA., Gold, C., (2014) Music therapy for people with autism spectrum disorder. Cochrane Database of Systematic Reviews, Issue 6. Art. No.: CD004381. https://doi.org/10.1002/14651858.CD004381.pub3.

Geretsegger, M., Mössler, K. A., Bieleninik, Ł., Chen, X. J., Heldal, T. O., & Gold, C. (2017) Music therapy for people with schizophrenia and schizophrenia-like disorders. The Cochrane Database of Systematic Reviews, 5(5), CD004025. https://doi.org/10.1002/14651858.CD004025.pub4

Gezginci, E., Goktas, S., & Orhan, B. N. (2020) The effects of environmental stressors in intensive care unit on anxiety and depression. Nursing in Critical Care, 10.1111/nicc.12553. https://doi.org/10.1111/nicc.12553

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., & Pitman, R. K. (2002) Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nature neuroscience, 5(11), 1242–1247. https://doi.org/10.1038/nn958

Gilbertson, M. W., Williston, S. K., Paulus, L. A., Lasko, N. B., Gurvits, T. V., Shenton, M. E., Pitman, R. K., & Orr, S. P. (2007) Configural cue performance in identical twins discordant for posttraumatic stress disorder: theoretical implications for the role of hippocampal function. Biological psychiatry, 62(5), 513–520. https://doi.org/10.1016/j.biopsych.2006.12.023

Girard, T. D., Shintani, A. K., Jackson, J. C., Gordon, S. M., Pun, B. T., Henderson, M. S., Dittus, R. S., Bernard, G. R., & Ely, E. W. (2007) Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. Critical Care (London, England), 11(1), R28. https://doi.org/10.1186/cc5708

Golden, T. L., Springs, S., Kimmel, H. J., Gupta, S., Tiedemann, A., Sandu, C. C., & Magsamen, S. (2021) The Use of Music in the Treatment and Management of Serious Mental Illness: A Global Scoping Review of the Literature. Frontiers in Psychology, 12, 649840. https://doi.org/10.3389/fpsyg.2021.649840

Gonzalez-Ojea, M. J., Dominguez-Lloria, S., Portela-Pino, I., & Alvarinas-Villaverde, M. (2021). Physical and Cognitive Functioning of Institutionalized Elderly People in Rural Areas. Preventive Actions Using Physical Activity and Music Therapy. *HEALTHCARE*, *9*(11), 1536. https://doi.org/10.3390/healthcare9111536

Gooding, L. F., & Langston, D. G. (2019). Music Therapy With Military Populations: A Scoping Review. *Journal of Music Therapy*, *56*(4), 315–347. https://doi.org.login.ezproxy.library.ualberta.ca/10.1093/jmt/thz010

Griffiths, J., Fortune, G., Barber, V., & Young, J. D. (2007) The prevalence of post-traumatic stress disorder in survivors of ICU treatment: a systematic review. Intensive Care Medicine, 33(9), 1506–1518. https://doi.org/10.1007/s00134-007-0730-z

Griffiths, J., Hatch, R. A., Bishop, J., Morgan, K., Jenkinson, C., Cuthbertson, B. H., & Brett, S. J. (2013). An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. *Critical Care (London, England)*, *17*(3), R100. https://doi.org/10.1186/cc12745

Grocke, D. E., & Wigram, T. (2007) Receptive methods in music therapy: techniques and clinical applications for music therapy clinicians, educators, and students. Jessica Kingsley Publishers.

Groussard, M., Viader, F., Landeau, B., Desgranges, B., Eustache, F., & Platel, H. (2014) The effects of musical practice on structural plasticity: the dynamics of grey matter changes. Brain and cognition, 90, 174–180. https://doi.org/10.1016/j.bandc.2014.06.013

Grupe, D. W., Hushek, B. A., Davis, K., Schoen, A. J., Wielgosz, J., Nitschke, J. B., & Davidson, R. J. (2019) Elevated perceived threat is associated with reduced hippocampal volume in combat veterans. Scientific Reports, 9(1), 14888. https://doi.org/10.1038/s41598-019-51533-x

Gullick, J. G., & Kwan, X. X. (2015) Patient-directed music therapy reduces anxiety and sedation exposure in mechanically ventilated patients: a research critique. Australian Critical Care: official journal of the Confederation of Australian Critical Care Nurses, 28(2), 103–105. https://doi.org/10.1016/j.aucc.2015.03.003

Gültekin, Y., Özçelik, Z., Akıncı, S. B., & Yorgancı, H. K. (2018) Evaluation of stressors in intensive care units. Turkish Journal of Surgery, 34(1), 5–8. https://doi.org/10.5152/turkjsurg.2017.3736

Guo, P., Li, Q., Wang, X., Li, X., Wang, S., Xie, Y., Xie, Y., Fu, Z., Zhang, X., & Li, S. (2020) Structural Covariance Changes of Anterior and Posterior Hippocampus During Musical Training in Young Adults. Frontiers in neuroanatomy, 14, 20. https://doi.org/10.3389/fnana.2020.00020)

Hackney, M. E., & Bennett, C. G. (2014). Dance therapy for individuals with Parkinson's disease: improving quality of life. *Research and Reviews in Parkinsonism*, *4*, 17-25.

Harlan, E. A., Miller, J., Costa, D. K., Fagerlin, A., Iwashyna, T. J., Chen, E. P., Lipman, K., & Valley, T. S. (2020). Emotional Experiences and Coping Strategies of Family Members of Critically Ill Patients. *Chest*, *158*(4), 1464–1472. https://doi.org/10.1016/j.chest.2020.05.535

Harvey, M. A., & Davidson, J. E. (2016). Postintensive Care Syndrome: Right Care, Right Now…and Later. *Critical Care Medicine*, *44*(2), 381–385. https://doi.org/10.1097/CCM.0000000000001531

Heiderscheit, A., Breckenridge, S. J., Chlan, L. L., & Savik, K. (2014) Music preferences of mechanically ventilated patients participating in a randomized controlled trial. *Music and medicine*, 6(2), 29–38. https://doi/10.47513/mmd.v6i2.177

Herman, J. P., McKlveen, J. M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., Scheimann, J., & Myers, B. (2016) Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. Comprehensive Physiology, 6(2), 603–621. https://doi.org/10.1002/cphy.c150015

Hetland, B., Lindquist, R., & Chlan, L. L. (2015) The influence of music during mechanical ventilation and weaning from mechanical ventilation: A review. Heart & Lung: The Journal of Critical Care, 44(5), 416–425. https://doi.org/10.1016/j.hrtlng.2015.06.010

Heyland, D. K., Davidson, J., Skrobik, Y., des Ordons, A. R., Van Scoy, L. J., Day, A. G., Vandall-Walker, V., & Marshall, A. P. (2018). Improving partnerships with family members of ICU patients: study protocol for a randomized controlled trial. *Trials*, *19*(1), 3. https://doi.org/10.1186/s13063-017-2379-4

Heyland, D. K., Hopman, W., Coo, H., Tranmer, J., & McColl, M. A. (2000). Long-term health-related quality of life in survivors of sepsis. Short Form 36: a valid and reliable measure of health-related quality of life. *Critical care medicine*, *28*(11), 3599–3605. https://doi.org/10.1097/00003246-200011000-00006

Hole, J., Hirsch, M., Ball, E., & Meads, C. (2015) Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis. Lancet (London, England), 386(10004), 1659–1671. https://doi.org/10.1016/S0140-6736(15)60169-6

Hosey, M. M., Leoutsakos, J. S., Li, X., Dinglas, V. D., Bienvenu, O. J., Parker, A. M., Hopkins, R. O., Needham, D. M., & Neufeld, K. J. (2019). Screening for posttraumatic stress disorder in ARDS survivors: validation of the Impact of Event Scale-6 (IES-6). *Critical care (London, England)*, *23*(1), 276. https://doi.org/10.1186/s13054-019-2553-z

Hua, M., Gong, M. N., Brady, J., & Wunsch, H. (2015). Early and late unplanned rehospitalizations for survivors of critical illness*. *Critical Care Medicine*, *43*(2), 430–438. https://doi.org/10.1097/CCM.0000000000000717

Imel Z. E., Laska K., Jakupcak M., Simpson T. L. (2013). Meta-analysis of dropout in treatments for posttraumatic stress disorder. *J. Consult. Clin. Psychol.* 81, 394–404. 10.1037/a0031474

Jackson, J. C., Ely, E. W., Morey, M. C., Anderson, V. M., Denne, L. B., Clune, J., Siebert, C. S., Archer, K. R., Torres, R., Janz, D., Schiro, E., Jones, J., Shintani, A. K., Levine, B., Pun, B. T., Thompson, J., Brummel, N. E., & Hoenig, H. (2012). Cognitive and physical rehabilitation of intensive care unit survivors: results of the RETURN randomized controlled pilot investigation. *Critical Care Medicine*, *40*(4), 1088–1097. https://doi.org/10.1097/CCM.0b013e3182373115

Jackson, J. C., Hart, R. P., Gordon, S. M., Hopkins, R. O., Girard, T. D., & Ely, E. W. (2007) Post-traumatic stress disorder and post-traumatic stress symptoms following critical illness in medical intensive care unit patients: assessing the magnitude of the problem. Critical Care (London, England), 11(1), R27. https://doi.org/10.1186/cc5707

Jackson, J. C., Pandharipande, P. P., Girard, T. D., Brummel, N. E., Thompson, J. L., Hughes, C. G., Pun, B. T., Vasilevskis, E. E., Morandi, A., Shintani, A. K., Hopkins, R. O., Bernard, G. R., Dittus, R. S., Ely, E. W., & Bringing to light the Risk Factors and Incidence of Neuropsychological dysfunction in ICU survivors (BRAIN-ICU) study investigators (2014). Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. *The Lancet. Respiratory Medicine*, *2*(5), 369–379. https://doi.org/10.1016/S2213-2600(14)70051-7

Jeong, Y. J., & Kang, J.. (2019). Development and validation of a questionnaire to measure post-intensive care syndrome. *Intensive and Critical Care Nursing*, *55*. https://doi /10.1016/j.iccn.2019.102756

Jezierska N. (2014). Psychological reactions in family members of patients hospitalised in intensive care units. *Anaesthesiology Intensive Therapy*, *46*(1), 42–45. https://doi.org/10.5603/AIT.2014.0009

Johnstone, T., van Reekum, C. M., Urry, H. L., Kalin, N. H., & Davidson, R. J. (2007) Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. The Journal of neuroscience: The official Journal of the Society for Neuroscience, 27(33), 8877–8884.

Jubran, A., Lawm, G., Duffner, L. A., Collins, E. G., Lanuza, D. M., Hoffman, L. A., & Tobin, M. J. (2010). Post-traumatic stress disorder after weaning from prolonged mechanical ventilation. *Intensive Care Medicine*, *36*(12), 2030–2037. https://doi /10.1007/s00134-010-1972-8

Jutte, J. E., Needham, D. M., Pfoh, E. R., & Bienvenu, O. J. (2015). Psychometric evaluation of the Hospital Anxiety and Depression Scale 3 months after acute lung injury. *Journal of critical care*, *30*(4), 793–798. https://doi.org/10.1016/j.jcrc.2015.04.006

Kaarlola, A., Pettilä, V., & Kekki, P. (2004). Performance of two measures of general health-related quality of life, the EQ-5D and the RAND-36 among critically ill patients. *Intensive care medicine*, *30*(12), 2245–2252. https://doi.org/10.1007/s00134-004-2471-6

Kamdar, B. B., Huang, M., Dinglas, V. D., Colantuoni, E., von Wachter, T. M., Hopkins, R. O., Needham, D. M., & National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network (2017). Joblessness and Lost Earnings after Acute Respiratory Distress Syndrome in a 1-Year National Multicenter Study. *American Journal of Respiratory and Critical Care Medicine*, *196*(8), 1012–1020. https://doi.org/10.1164/rccm.201611-2327OC.

Kang, J., Jeong, Y. J., & Hong, J. (2020). Cut-Off Values of the Post-Intensive Care Syndrome Questionnaire for the Screening of Unplanned Hospital Readmission within One Year. *Journal of Korean Academy of Nursing*, *50*(6), 787–798. https://doi.org/10.4040/jkan.20233

Karanikola, M., Alexandrou, G., Mpouzika, M., Chatzittofis, A., Kusi, A. E., & Papathanassoglou, E. (2021). Pilot exploration of post-traumatic stress symptoms in intensive care unit survivors in Cyprus. *Nursing in Critical Care*, *26*(2), 109–117. https://doi /10.1111/nicc.12574

Kentish-Barnes, N., Chaize, M., Seegers, V., Legriel, S., Cariou, A., Jaber, S., Lefrant, J. Y., Floccard, B., Renault, A., Vinatier, I., Mathonnet, A., Reuter, D., Guisset, O., Cohen-Solal, Z., Cracco, C., Seguin, A., Durand-Gasselin, J., Éon, B., Thirion, M., Rigaud, J. P., … Azoulay, É. (2015). Complicated grief after death of a relative in the intensive care unit. *The European respiratory journal*, *45*(5), 1341–1352. https://doi.org/10.1183/09031936.00160014

Kentish-Barnes, N., Chevret, S., Champigneulle, B., Thirion, M., Souppart, V., Gilbert, M., Lesieur, O., Renault, A., Garrouste-Orgeas, M., Argaud, L., Venot, M., Demoule, A., Guisset, O., Vinatier, I., Troché, G., Massot, J., Jaber, S., Bornstain, C., Gaday, V., Robert, R., Famirea Study Group (2017). Effect of a condolence letter on grief symptoms among relatives of patients who died in the ICU: a randomized clinical trial. *Intensive Care Medicine*, *43*(4), 473–484. https://doi.org/10.1007/s00134-016-4669-9

Kentish-Barnes, N., Seegers, V., Legriel, S., Cariou, A., Jaber, S., Lefrant, J.-Y., Floccard, B., Renault, A., Vinatier, I., Mathonnet, A., Reuter, D., Guisset, O., Cracco, C., Seguin, A., Durand-Gasselin, J., Éon, B., Thirion, M., Rigaud, J.-P., Philippon-Jouve, B., … Azoulay,

E. (2016). CAESAR: a new tool to assess relatives' experience of dying and death in the ICU. *Intensive Care Medicine*, *42*(6), 995–1002. https://doi /10.1007/s00134-016-4260-4

Khan, S. H., Kitsis, M., Golovyan, D., Wang, S., Chlan, L. L., Boustani, M., & Khan, B. A. (2018) Effects of music intervention on inflammatory markers in critically ill and post-operative patients: A systematic review of the literature. Heart & Lung: The Journal of Critical Care, 47(5), 489–496. https://doi.org/10.1016/j.hrtlng.2018.05.015

Khoudri, I., Ali Zeggwagh, A., Abidi, K., Madani, N., & Abouqal, R. (2007). Measurement properties of the short form 36 and health-related quality of life after intensive care in Morocco. *Acta anaesthesiologica Scandinavica*, *51*(2), 189–197. https://doi.org/10.1111/j.1399-6576.2006.01225.x

Khoudri, I., Belayachi, J., Dendane, T., Abidi, K., Madani, N., Zekraoui, A., Zeggwagh, A. A., & Abouqal, R. (2012). Measuring quality of life after intensive care using the Arabic version for Morocco of the EuroQol 5 Dimensions. *BMC research notes*, *5*, 56. https://doi.org/10.1186/1756-0500-5-56

Kim, E. J., Pellman, B., & Kim, J. J. (2015) Stress effects on the hippocampus: a critical review. Learning & memory (Cold Spring Harbor, N.Y.), 22(9), 411–416. https://doi.org/10.1101/lm.037291.114

Kim, J. J., & Yoon, K. S. (1998) Stress: metaplastic effects in the hippocampus. Trends in neurosciences, 21(12), 505–509. https://doi.org/10.1016/s0166-2236(98)01322-8

Koelsch S. (2014) Brain correlates of music-evoked emotions. Nature reviews. Neuroscience, 15(3), 170–180. https://doi.org/10.1038/nrn3666

Koelsch S. (2020) A coordinate-based meta-analysis of music-evoked emotions. NeuroImage, 223, 117350. https://doi.org/10.1016/j.neuroimage.2020.117350

Koelsch, S. (2010) Towards a neural basis of music-evoked emotions. Trends in Cognitive Sciences, 14(3), 131–137. https://doi.org/10.1016/j.tics.2010.01.002

Koelsch, S. Emotion and Music. In J. Armony & P. Vuilleumier (Eds.), (2013) The Cambridge Handbook of Human Affective Neuroscience (pp. 286-303). Cambridge: Cambridge University Press. https://doi:10.1017/CBO9780511843716.016

Koelsch, S., & Skouras, S. (2014) Functional centrality of amygdala, striatum, and hypothalamus in a "small-world" network underlying joy: an fMRI study with music. Human brain mapping, 35(7), 3485–3498. https://doi.org/10.1002/hbm.22416

Koelsch, S., Fuermetz, J., Sack, U., Bauer, K., Hohenadel, M., Wiegel, M., Kaisers, U. X., & Heinke, W. (2011) Effects of Music Listening on Cortisol Levels and Propofol Consumption during Spinal Anesthesia. Frontiers in Psychology, 2, 58. https://doi.org/10.3389/fpsyg.2011.00058

Koelsch, S., Skouras, S., Fritz, T., Herrera, P., Bonhage, C., Küssner, M. B., & Jacobs, A. M. (2013) The roles of superficial amygdala and auditory cortex in music-evoked fear and joy. NeuroImage, 81, 49–60. https://doi.org/10.1016/j.neuroimage.2013.05.008 [CD-recorded pieces from various epochs and styles

Kogutek, D. L., Holmes, J. D., Grahn, J. A., Lutz, S. G., & Ready, E. (2016). Active Music Therapy and Physical Improvements From Rehabilitation for Neurological Conditions. *Advances in mind-body medicine*, *30*(4), 14–22.

Kress, J. P., & Hall, J. B. (2014). ICU-acquired weakness and recovery from critical illness. *The New England Journal of Medicine*, *370*(17), 1626–1635. https://doi.org/10.1056/NEJMra1209390

Kross, E. K., Engelberg, R. A., Gries, C. J., Nielsen, E. L., Zatzick, D., & Curtis, J. R. (2011). ICU care associated with symptoms of depression and posttraumatic stress disorder among family members of patients who die in the ICU. *Chest*, *139*(4), 795–801. https://doi.org/10.1378/chest.10-0652

Landis-Shack, N., Heinz, A. J., & Bonn-Miller, M. O. (2017). Music Therapy for Posttraumatic Stress in Adults: A Theoretical Review. *Psychomusicology*, *27*(4), 334–342. https://doi.org/10.1037/pmu0000192

Lasiter, S., Oles, S. K., Mundell, J., London, S., & Khan, B. (2016). Critical Care Follow-up Clinics: A Scoping Review of Interventions and Outcomes. *Clinical Nurse Specialist CNS*, *30*(4), 227–237. https://doi.org/10.1097/NUR.0000000000000219

Laura S. Sakka, & Suvi Saarikallio. (2020) Spontaneous Music-Evoked Autobiographical Memories in Individuals Experiencing Depression. *Music & Science*, *3*. https://doi/10.1177/2059204320960575

Lee, M., Kang, J., & Jeong, Y. J. (2020) Risk factors for post-intensive care syndrome: A systematic review and meta-analysis. Australian Critical Care, 33(3), 287–294 https://doi.org/10.1016/j.aucc.2019.10.004

Levac, D., Colquhoun, H., & O'Brien, K. K. (2010). Scoping studies: advancing the methodology. *Implementation Science: IS*, *5*, 69. https://doi.org/10.1186/1748-5908-5-69

Liu, T., Ke, J., Qi, R., Zhang, L., Zhang, Z., Xu, Q., Zhong, Y., Lu, G., & Chen, F. (2021) Altered functional connectivity of the amygdala and its subregions in typhoon-related post-traumatic stress disorder. Brain & Behavior, 11(1), 1–15. https://doi-org /10.1002/brb3.1952

Lucas, N. P., Macaskill, P., Irwig, L., & Bogduk, N. (2010). The development of a quality appraisal tool for studies of diagnostic reliability (QAREL). *Journal of Clinical Epidemiology*, *63*(8), 854–861. https://doi.org/10.1016/j.jclinepi.2009.10.002.

Lynch, K. A., Emard, N., Liou, K. T., Popkin, K., Borten, M., Nwodim, O., Atkinson, T. M., & Mao, J. J. (2021) Patient Perspectives on Active vs. Passive Music Therapy for Cancer in the Inpatient Setting: A Qualitative Analysis. Journal of pain and symptom management, , 62(1), 58–65. https://doi.org/10.1016

Maack, C. (2012) Outcomes and Processes of the Bonny Method of Guided Imagery and Music (GIM) and its Adaptations and Psychodynamic Imaginative Trauma Therapy (PITT) for Women with Complex PTSD. Thesis submitted for the degree of Doctor of Philosophy, Aalborg University, Denmark,. https://vbn.aau.dk/ws/portalfiles/portal/68395912/Carola_Maack_12.pdf

Macfarlane, C., Masthoff, E., & Hakvoort, L. (2019) Short-Term Music Therapy Attention and Arousal Regulation Treatment (SMAART) for Prisoners with Posttraumatic Stress Disorder: A Feasibility Study. Journal of Forensic Psychology Research & Practice, 19(5), 376–392. https://doi/10.1080/24732850.2019.1670023

Magee, W. L., Clark, I., Tamplin, J., & Bradt, J. (2017) Music interventions for acquired brain injury. The Cochrane Database of Systematic Reviews, 1(1), CD006787. https://doi.org/10.1002/14651858.CD006787.pub3

Mary, A., Dayan, J., Leone, G., Postel, C., Fraisse, F., Malle, C., Vallée, T., Klein-Peschanski, C., Viader, F., de la Sayette, V., Peschanski, D., Eustache, F., & Gagnepain, P. (2020) Resilience after trauma: The role of memory suppression. *Science (New York, N.Y.)*, , *367*(6479), eaay8477. https://doi.org/10.1126/science.aay8477

Matsuo, K., Taneichi, K., Matsumoto, A., Ohtani, T., Yamasue, H., Sakano, Y., Sasaki, T., Sadamatsu, M., Kasai, K., Iwanami, A., Asukai, N., Kato, N., & Kato, T. (2003) Hypoactivation of the prefrontal cortex during verbal fluency test in PTSD: a near-infrared spectroscopy study. Psychiatry Research, 124(1), 1–10. https://doi.org/10.1016/s0925-4927(03)00093-3

Mavridis I. N. (2015) Music and the nucleus accumbens. Surgical and radiologic anatomy: SRA, 37(2), 121–125. https://doi.org/10.1007/s00276-014-1360-0

McAuley, M.T., Kenny, R.A., Kirkwood, T.B., Wilkinson, D.J., Jones, J.J., & Miller, V.M. (2009) A mathematical model of aging-related and cortisol induced hippocampal dysfunction. BMC Neurosci, 10(26). doi:10.1186/1471-2202-10-26

McFarlane A. C. (2010) The long-term costs of traumatic stress: intertwined physical and psychological consequences. World Psychiatry: Official Journal of the World Psychiatric Association (WPA), 9(1), 3–10. https://doi.org/10.1002/j.2051-5545.2010.tb00254

McGiffin, J. N., Galatzer-Levy, I. R., & Bonanno, G. A. (2016) Is the intensive care unit traumatic? What we know and don't know about the intensive care unit and posttraumatic stress responses. Rehabilitation Psychology, 61(2), 120–131. https://doi.org/10.1037/rep0000073

McIlroy, P. A., King, R. S., Garrouste-Orgeas, M., Tabah, A., & Ramanan, M. (2019). The Effect of ICU Diaries on Psychological Outcomes and Quality of Life of Survivors of Critical Illness and Their Relatives: A Systematic Review and Meta-Analysis. *Critical Care Medicine*, *47*(2), 273–279. https://doi.org/10.1097/CCM.0000000000003547

McKinney, C. H., & Honig, T. J. (2017) Health Outcomes of a Series of Bonny Method of Guided Imagery and Music Sessions: A Systematic Review. Journal of Music Therapy, 54(1), 1–34. https://doi.org/10.1093/jmt/thw016

Mclntosh, G. & Thaut, M. (2010). How music helps to heal the injured brain: Therapeutic use crescendos thanks to advances in brain science. The Dana Foundation. Available online: http://www.dana.org/Cerebrum/Default.aspx?id=39437 (accessed on 13 November 2021)

McNerney, M. W., Sheng, T., Nechvatal, J. M., Lee, A. G., Lyons, D. M., Soman, S., Liao, C. P., O'Hara, R., Hallmayer, J., Taylor, J., Ashford, J. W., Yesavage, J., & Adamson, M. M. (2018) Integration of neural and epigenetic contributions to posttraumatic stress symptoms: The role of hippocampal volume and glucocorticoid receptor gene methylation. PloS one, 13(2), e0192222. https://doi.org/10.1371/journal.pone.0192222

Mikkelsen, M. E., Still, M., Anderson, B. J., Bienvenu, O. J., Brodsky, M. B., Brummel, N., Butcher, B., Clay, A. S., Felt, H., Ferrante, L. E., Haines, K. J., Harhay, M. O., Hope, A. A., Hopkins, R. O., Hosey, M., Hough, C. "Terri" L., Jackson, J. C., Johnson, A., Khan, B., … Sevin, C. M. (2020). Society of Critical Care Medicine's International Consensus Conference on Prediction and Identification of Long-Term Impairments After Critical Illness. *Critical Care Medicine*. https://doi.org/10.1097/CCM.0000000000004586

Milton, A., Brück, E., Schandl, A., Bottai, M., & Sackey, P. (2017). Early psychological screening of intensive care unit survivors: a prospective cohort study. *Critical care (London, England)*, *21*(1), 273. https://doi.org/10.1186/s13054-017-1813-z

Milton, A., Schandl, A., Soliman, I. W., Meijers, K., van den Boogaard, M., Larsson, I. M., Brorsson, C., Östberg, U., Oxenbøll-Collet, M., Savilampi, J., Paskins, S., Bottai, M., & Sackey, P. V. (2018). Development of an ICU discharge instrument predicting

psychological morbidity: a multinational study. *Intensive care medicine*, *44*(12), 2038–2047. https://doi.org/10.1007/s00134-018-5467-3

Milton, A., Schandl, A., Soliman, I., Joelsson-Alm, E., van den Boogaard, M., Wallin, E., Brorsson, C., Östberg, U., Latocha, K., Savilampi, J., Paskins, S., Bottai, M., & Sackey, P. (2020). ICU discharge screening for prediction of new-onset physical disability-A multinational cohort study. *Acta anaesthesiologica Scandinavica*, *64*(6), 789–797. https://doi.org/10.1111/aas.13563

Mitchell, M. L., Shum, D., Mihala, G., Murfield, J. E., & Aitken, L. M. (2018). Long-term cognitive impairment and delirium in intensive care: A prospective cohort study. *Australian critical care : official journal of the Confederation of Australian Critical Care Nurses*, *31*(4), 204–211. https://doi.org/10.1016/j.aucc.2017.07.002

Mofredj, A., Alaya, S., Tassaioust, K., Bahloul, H., & Mrabet, A. (2016) Music therapy, a review of the potential therapeutic benefits for the critically ill. Journal of Critical Care, 35, 195–199. https://doi.org/10.1016/j.jcrc.2016.05.021.

Moore, K. S. (2013) A systematic review on the neural effects of music on emotion regulation: Implications for music therapy practice. *Journal of Music Therapy*, 50(3), 198-242. https://doi/doi:10.1093/jmt/50.3.198

Moreno-Morales, C., Calero, R., Moreno-Morales, P., & Pintado, C. (2020). Music Therapy in the Treatment of Dementia: A Systematic Review and Meta-Analysis. *Frontiers in medicine*, *7*, 160. https://doi.org/10.3389/fmed.2020.00160

Moumdjian, L., Sarkamo, T., Leone, C., Leman, M., & Feys, P. (2017). Effectiveness of music-based interventions on motricity or cognitive functioning in neurological populations: a

systematic review. *European journal of physical and rehabilitation medicine*, *53*(3), 466–482. https://doi.org/10.23736/S1973-9087.16.04429-4

Munn, Z., Peters, M., Stern, C., Tufanaru, C., McArthur, A., & Aromataris, E. (2018). Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Medical Research Methodology*, *18*(1), 143. https://doi.org/10.1186/s12874-018-0611-x

Myers, B., McKlveen, J. M., & Herman, J. P. (2014) Glucocorticoid actions on synapses, circuits, and behavior: implications for the energetics of stress. Frontiers in neuroendocrinology, 35(2), 180–196. https://doi.org/10.1016/j.yfrne.2013.12.003

Needham, D. M., Davidson, J., Cohen, H., Hopkins, R. O., Weinert, C., Wunsch, H., Zawistowski, C., Bemis-Dougherty, A., Berney, S. C., Bienvenu, O. J., Brady, S. L., Brodsky, M. B., Denehy, L., Elliott, D., Flatley, C., Harabin, A. L., Jones, C., Louis, D., Meltzer, W., … Harvey, M. A. (2012). Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Critical Care Medicine*, *40*(2), 502–509. https://doi.org/10.1097/CCM.0b013e318232da75

Needham, D. M., Sepulveda, K. A., Dinglas, V. D., Chessare, C. M., Friedman, L. A., Bingham, C. O., 3rd, & Turnbull, A. E. (2017). Core Outcome Measures for Clinical Research in Acute Respiratory Failure Survivors. An International Modified Delphi Consensus Study. *American journal of respiratory and critical care medicine*, *196*(9), 1122–1130. https://doi.org/10.1164/rccm.201702-0372OC

Needham, D. M., Wozniak, A. W., Hough, C. L., Morris, P. E., Dinglas, V. D., Jackson, J. C., Mendez-Tellez, P. A., Shanholtz, C., Ely, E. W., Colantuoni, E., Hopkins, R. O., & National Institutes of Health NHLBI ARDS Network (2014). Risk factors for physical

impairment after acute lung injury in a national, multicenter study. *American Journal of Respiratory and Critical Care Medicine*, *189*(10), 1214–1224. https://doi.org/10.1164/rccm.201401-0158OC

Nickel, M., Nickel, C., Mitterlehner, F., Rother, W., Leiberich, P., Tritt, K., & Loew, T.. (n.d.). The occurrence of posttraumatic stress disorder in patients following intensive care treatment: A cross-sectional study in a random sample. *Journal of Intensive Care Medicine*, *19*(5), 285–290. https://doi /10.1177/0885066604267684

Nickel, T. (2011). Trauma: HPA Axis [Video]. Available online: https://www.youtube.com/watch?v=otLHMbNyUx0 (accessed on 13 November 2021)

Nielsen, A. H., Angel, S., Egerod, I., Lund, T. H., Renberg, M., & Hansen, T. B. (2020). The effect of family-authored diaries on posttraumatic stress disorder in intensive care unit patients and their relatives: A randomised controlled trial (DRIP-study). *Australian Critical Care: official Journal of the Confederation of Australian Critical Care Nurses*, *33*(2), 123–129. https://doi.org/10.1016/j.aucc.2019.01.004

Oeyen, S. G., Vandijck, D. M., Benoit, D. D., Annemans, L., & Decruyenaere, J. M. (2010). Quality of life after intensive care: a systematic review of the literature. *Critical Care Medicine*, *38*(12), 2386–2400. https://doi.org/10.1097/CCM.0b013e3181f3dec5

Ohtake, P. J., Lee, A. C., Scott, J. C., Hinman, R. S., Ali, N. A., Hinkson, C. R., Needham, D. M., Shutter, L., Smith-Gabai, H., Spires, M. C., Thiele, A., Wiencek, C., & Smith, J. M. (2018). Physical Impairments Associated With Post-Intensive Care Syndrome: Systematic Review Based on the World Health Organization's International Classification of Functioning, Disability and Health Framework. *Physical therapy*, *98*(8), 631–645. https://doi.org/10.1093/ptj/pzy059

Olszewska, A. M., Gaca, M., Herman, A. M., Jednoróg, K., & Marchewka, A. (2021) How Musical Training Shapes the Adult Brain: Predispositions and Neuroplasticity. Frontiers in neuroscience, 15, 630829. https://doi.org/10.3389/fnins.2021.630829

Paintain, E., & Cassidy, S. (2018). First-line therapy for post-traumatic stress disorder: A systematic review of cognitive behavioural therapy and psychodynamic approaches. *Counselling and psychotherapy research*, *18*(3), 237–250. https://doi.org/10.1002/capr.12174

Pandharipande, P. P., Girard, T. D., Jackson, J. C., Morandi, A., Thompson, J. L., Pun, B. T., Brummel, N. E., Hughes, C. G., Vasilevskis, E. E., Shintani, A. K., Moons, K. G., Geevarghese, S. K., Canonico, A., Hopkins, R. O., Bernard, G. R., Dittus, R. S., Ely, E. W., & BRAIN-ICU Study Investigators (2013). Long-term cognitive impairment after critical illness. *The New England Journal of Medicine*, *369*(14), 1306–1316. https://doi.org/10.1056/NEJMoa1301372

Parada-Cabaleiro, E., Batliner, A., & Schedl, M. (2022) An Exploratory Study on the Acoustic Musical Properties to Decrease Self-Perceived Anxiety. *International journal of environmental research and public health*, 19(2), 994. https://doi.org/10.3390/ijerph19020994

Parker, A. M., Sricharoenchai, T., Raparla, S., Schneck, K. W., Bienvenu, O. J., & Needham, D. M. (2015). Posttraumatic stress disorder in critical illness survivors: a metaanalysis. *Critical Care Medicine*, *43*(5), 1121–1129. https://doi.org/10.1097/CCM.0000000000000882

Parsons, E. C., Palen, B., Hough, C. L., Vitiello, M. V., Zatzick, D., & Davydow, D. S.. (n.d.). Validity of a single PTSD checklist item to screen for insomnia in survivors of critical illness. *Heart and Lung*, *47*(2), 87–92. https://doi /10.1016/j.hrtlng.2017.12.006

Patrick, D. L., Danis, M., Southerland, L. I., & Hong, G. (1988). Quality of life following intensive care. *Journal of general internal medicine*, *3*(3), 218–223. https://doi.org/10.1007/BF02596335

Perkins, R., Mason-Bertrand, A., Fancourt, D., Baxter, L., & Williamon, A. (2020) How Participatory Music Engagement Supports Mental Well-being: A Meta-Ethnography. Qualitative Health Research, 30(12), 1924–1940. https://doi.org/10.1177/1049732320944142

Pfoh, E. R., Chan, K. S., Dinglas, V. D., Girard, T. D., Jackson, J. C., Morris, P. E., Hough, C. L., Mendez-Tellez, P. A., Ely, E. W., Huang, M., Needham, D. M., Hopkins, R. O., & NIH NHLBI ARDS Network (2015). Cognitive screening among acute respiratory failure survivors: a cross-sectional evaluation of the Mini-Mental State Examination. *Critical care (London, England)*, *19*(1), 220. https://doi.org/10.1186/s13054-015-0934-5

Postel, C., Mary, A., Dayan, J., Fraisse, F., Vallée, T., Guillery-Girard, B., Viader, F., Sayette, V., Peschanski, D., Eustache, F., & Gagnepain, P. (2021) Variations in response to trauma and hippocampal subfield changes. Neurobiology of Stress, 15, 100346. https://doi.org/10.1016/j.ynstr.2021.100346

Pourmovahed, Z., Yassini Ardekani, S. M., Roozbeh, B., & Ezabad, A. R. (2021) The Effect of Non-verbal Music on Posttraumatic Stress Disorder in Mothers of Premature Neonates. Iranian Journal of Nursing and Midwifery Research, 26(2), 150–153. https://doi.org/10.4103/ijnmr.IJNMR_37_20

Pun, B. T., Balas, M. C., Barnes-Daly, M. A., Thompson, J. L., Aldrich, J. M., Barr, J., Byrum, D., Carson, S. S., Devlin, J. W., Engel, H. J., Esbrook, C. L., Hargett, K. D., Harmon, L., Hielsberg, C., Jackson, J. C., Kelly, T. L., Kumar, V., Millner, L., Morse, A., Perme, C. S., … Ely, E. W. (2019). Caring for Critically Ill Patients with the ABCDEF Bundle: Results of the ICU Liberation Collaborative in Over 15,000 Adults. *Critical care medicine*, *47*(1), 3–14. https://doi.org/10.1097/CCM.0000000000003482

Rabiee, A., Nikayin, S., Hashem, M. D., Huang, M., Dinglas, V. D., Bienvenu, O. J., ... & Needham, D. M. (2016). Depressive symptoms after critical illness: a systematic review and meta-analysis. *Critical Care Medicine*, *44*(9), 1744-1753. https://doi:10.1097/CCM.0000000000001811

Rawal, G., Yadav, S., & Kumar, R. (2017). Post-intensive Care Syndrome: an Overview. *Journal of Translational Internal Medicine*, *5*(2), 90–92. https://doi.org/10.1515/jtim-2016-0016

Rengel, K. F., Hayhurst, C. J., Pandharipande, P. P., & Hughes, C. G. (2019). Long-term Cognitive and Functional Impairments After Critical Illness. *Anesthesia and analgesia*, *128*(4), 772–780. https://doi.org/10.1213/ANE.0000000000004066

Reybrouck, M., Vuust, P., & Brattico, E. (2018) Music and brain plasticity: how sounds trigger neurogenerative adaptations. Neuroplasticity Insights of Neural Reorganization, 85. http://doi.org/10.5772/intechopen.74318

Righy, C., Rosa, R. G., da Silva, R., Kochhann, R., Migliavaca, C. B., Robinson, C. C., Teche, S. P., Teixeira, C., Bozza, F. A., & Falavigna, M. (2019). Prevalence of post-traumatic stress disorder symptoms in adult critical care survivors: a systematic review and meta-analysis. *Critical care (London, England)*, *23*(1), 213. https://doi.org/10.1186/s13054-019-2489-3

Rosendahl, J., Kisyova, H., Gawlytta, R., & Scherag, A.. (n.d.). Comparative validation of three screening instruments for posttraumatic stress disorder after intensive care. *Journal of Critical Care*, *53*, 149–154. https://doi /10.1016/j.jcrc.2019.06.016

Rousseau, A. F., Prescott, H. C., Brett, S. J., Weiss, B., Azoulay, E., Creteur, J., Latronico, N., Hough, C. L., Weber-Carstens, S., Vincent, J. L., & Preiser, J. C. (2021). Long-term outcomes after critical illness: recent insights. *Critical care (London, England)*, *25*(1), 108. https://doi.org/10.1186/s13054-021-03535-3

Rudstam, G., Elofsson, U., Søndergaard, H. P., & Beck, B. D. (2017) Trauma-focused group music and imagery with women suffering from PTSD/complex PTSD: a feasibility study. Approaches. Music Therapy and Special Education, 9(2), 202-216.

Ruhl, A. P., Lord, R. K., Panek, J. A., Colantuoni, E., Sepulveda, K. A., Chong, A., Dinglas, V. D., Shanholtz, C. B., Pronovost, P. J., Steinwachs, D. M., & Needham, D. M. (2015). Health care resource use and costs of two-year survivors of acute lung injury. An observational cohort study. *Annals of the American Thoracic Society*, *12*(3), 392–401. https://doi.org/10.1513/AnnalsATS.201409-422OC

Schaefer H. E. (2017) Music-Evoked Emotions-Current Studies. Frontiers in neuroscience, 11, 600. https://doi.org/10.3389/fnins.2017.00600

Schandl, A., Bottai, M., Hellgren, E., Sundin, O., & Sackey, P. V. (2013). Developing an early screening instrument for predicting psychological morbidity after critical illness. *Critical care (London, England)*, *17*(5), R210. https://doi.org/10.1186/cc13018

Schandl, A., Bottai, M., Holdar, U., Hellgren, E., & Sackey, P. (2014). Early prediction of new-onset physical disability after intensive care unit stay: a preliminary instrument. *Critical care (London, England)*, *18*(4), 455. https://doi.org/10.1186/s13054-014-0455-7

Schoenfeld, T. J., & Gould, E. (2012) Stress, stress hormones, and adult neurogenesis. Experimental Neurology, 233(1), 12–21. https://doi.org/10.1016/j.expneurol.2011.01.008

Scragg, P., Jones, A., & Fauvel, N. (2001). Psychological problems following ICU treatment*. *Anaesthesia*, *56*(1), 9–14.

Selemon, L. D., Young, K. A., Cruz, D. A., & Williamson, D. E. (2019) Frontal Lobe Circuitry in Posttraumatic Stress Disorder. Chronic Stress. https://doi.org/10.1177/2470547019850166

Sheerin, C. M., Lind, M. J., Bountress, K. E., Marraccini, M. E., Amstadter, A. B., Bacanu, S. A., & Nugent, N. R. (2020) Meta-Analysis of Associations Between Hypothalamic-Pituitary-Adrenal Axis Genes and Risk of Posttraumatic Stress Disorder. Journal of traumatic stress, 33(5), 688–698. https://doi.org/10.1002/jts.22484

Sherin, J. E., & Nemeroff, C. B. (2011) Post-traumatic stress disorder: the neurobiological impact of psychological trauma. Dialogues in Clinical Neuroscience, 13(3), 263–278

Silveira, L., Silva, J., Soler, J., Sun, C., Tanaka, C., & Fu, C. (2018). Assessing functional status after intensive care unit stay: the Barthel Index and the Katz Index. *International journal for quality in health care : journal of the International Society for Quality in Health Care*, *30*(4), 265–270. https://doi.org/10.1093/intqhc/mzx203

Smith M. E. (2005) Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: a meta-analysis of structural MRI studies. Hippocampus, 15(6), 798–807. https://doi.org/10.1002/hipo.20102

Spies, C. D., Krampe, H., Paul, N., Denke, C., Kiselev, J., Piper, S. K., Kruppa, J., Grunow, J. J., Steinecke, K., Gülmez, T., Scholtz, K., Rosseau, S., Hartog, C., Busse, R., Caumanns, J., Marschall, U., Gersch, M., Apfelbacher, C., Weber-Carstens, S., & Weiss, B. (2021).

Instruments to measure outcomes of post-intensive care syndrome in outpatient care settings - Results of an expert consensus and feasibility field test. *Journal of the Intensive Care Society*, *22*(2), 159–174. https://doi.org/10.1177/1751143720923597

Spinazzola, J., Blaustein, M., & van der Kolk, B. A. (2005). Posttraumatic stress disorder treatment outcome research: The study of unrepresentative samples? Journal of Traumatic Stress,18,425–436. doi:10.1002/jts.20050

Stapleton, K. (2020). Music and Dementia: From Cognition to Therapy. *Journal of Sociology & Social Welfare*, *47*(3), 219–222.

Stevens, J. S., Jovanovic, T., Fani, N., Ely, T. D., Glover, E. M., Bradley, B., & Ressler, K. J. (2013) Disrupted amygdala-prefrontal functional connectivity in civilian women with posttraumatic stress disorder. Journal of Psychiatric Research, 47(10), 1469–1478. https://doi.org/10.1016/j.jpsychires.2013.05.031

Stoll, C., Kapfhammer, H. P., Rothenhäusler, H. B., Haller, M., Briegel, J., Schmidt, M., Krauseneck, T., Durst, K., & Schelling, G. (1999). Sensitivity and specificity of a screening test to document traumatic experiences and to diagnose post-traumatic stress disorder in ARDS patients after intensive care treatment. *Intensive Care Medicine*, *25*(7), 697–704. https://doi /10.1007/s001340050932

Story, K. M. & Beck, B. D. (2017) Guided Imagery and Music with female military veterans: An intervention development study. Arts in Psychotherapy, 55, 93–102. https://doi-org/10.1016/j.aip.2017.05.003

Stress and the brain. Available online: https://turnaroundusa.org/wp-content/uploads/2020/03/Stress-and-the-Brain_Turnaround-for-Children-032420.pdf (accessed on 13 November 2021)

Sukantarat, K. T., Williamson, R. C., & Brett, S. J. (2007). Psychological assessment of ICU survivors: a comparison between the Hospital Anxiety and Depression scale and the Depression, Anxiety and Stress scale. *Anaesthesia*, *62*(3), 239–243. https://doi.org/10.1111/j.1365-2044.2006.04948.x

Tan, X., Yowler, C. J., Super, D. M., & Fratianne, R. B. (2012) The interplay of preference, familiarity and psychophysical properties in defining relaxation music. *Journal of Music Therapy*, 49(2), 150-179. https://doi/doi:10.1093/jmt/49.2.150

Tian, Z. M., & Reis Miranda, D. (1995). Quality of life after intensive care with the sickness impact profile. *Intensive Care Medicine*, *21*(5), 422–428. https://doi /10.1007/bf01707411

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., Lewin, S., … Straus, S. E. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of internal medicine*, *169*(7), 467–473. https://doi.org/10.7326/M18-0850

Twigg, E., Humphris, G., Jones, C., Griffiths, R. D., & Bramwell, R.. (n.d.). Use of a screening questionnaire for post-traumatic stress disorder (PTSD) on a sample of UK ICU patients. *Acta Anaesthesiologica Scandinavica*, *52*(2), 202–208. https://doi /10.1111/j.1399-6576.2007.01531.x

Umberger R. (2019). What is the best core measure after critical illness when the IES-R is no longer accessible for new researchers?. *Critical care (London, England)*, *23*(1), 313. https://doi.org/10.1186/s13054-019-2595-2

Umbrello, M., Sorrenti, T., Mistraletti, G., Formenti, P., Chiumello, D., & Terzoni, S. (2019) Music therapy reduces stress and anxiety in critically ill patients: a systematic review of randomized clinical trials. Minerva Anestesiologica, 85(8), 886–898. https://doi /10.23736/S0375-9393.19.13526-2

Urry, H. L., van Reekum, C. M., Johnstone, T., Kalin, N. H., Thurow, M. E., Schaefer, H. S., Jackson, C. A., Frye, C. J., Greischar, L. L., Alexander, A. L., & Davidson, R. J. (2006) Amygdala, and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. The Journal of neuroscience: The Official Journal of the Society for Neuroscience, 26(16), 4415–4425. https://doi.org/10.1523/JNEUROSCI.3215-05.2006

van den Born-van Zanten, S. A., Dongelmans, D. A., Dettling-Ihnenfeldt, D., Vink, R., & van der Schaaf, M. (2016). Caregiver strain and posttraumatic stress symptoms of informal caregivers of intensive care unit survivors. *Rehabilitation Psychology*, *61*(2), 173–178. https://doi.org/10.1037/rep0000081

van der Steen, J. T., van Soest-Poortvliet, M. C., van der Wouden, J. C., Bruinsma, M. S., Scholten, R. J., & Vink, A. C. (2017) Music-based therapeutic interventions for people with dementia. The Cochrane Database of Systematic Reviews, 5(5), CD003477. https://doi.org/10.1002/14651858.CD003477

van Rooij, S. J. H., Kennis, M., Sjouwerman, R., van den Heuvel, M. P., Kahn, R. S., & Geuze, E. (2015) Smaller hippocampal volume as a vulnerability factor for the persistence of post-traumatic stress disorder. Psychological Medicine, 45(13), 2737–2746. https://doi /10.1017/S0033291715000707

Wade, D. F., Moon, Z., Windgassen, S. S., Harrison, A. M., Morris, L., & Weinman, J. A. (2016). Non-pharmacological interventions to reduce ICU-related psychological distress: a systematic review. *Minerva Anestesiologica*, *82*(4), 465–478.

Wade, D. M., Mouncey, P. R., Richards-Belle, A., Wulff, J., Harrison, D. A., Sadique, M. Z., Grieve, R. D., Emerson, L. M., Mason, A. J., Aaronovitch, D., Als, N., Brewin, C. R., Harvey, S. E., Howell, D., Hudson, N., Mythen, M. G., Smyth, D., Weinman, J., Welch, J., Whitman, C., … POPPI Trial Investigators (2019). Effect of a Nurse-Led Preventive Psychological Intervention on Symptoms of Posttraumatic Stress Disorder Among Critically Ill Patients: A Randomized Clinical Trial. *JAMA*, *321*(7), 665–675. https://doi.org/10.1001/jama.2019.0073

Wade, D., Hardy, R., Howell, D., & Mythen, M. (2013) Identifying clinical and acute psychological risk factors for PTSD after critical care: a systematic review. Minerva Anestesiologica, 79(8), 944–963.

Wang, S., & Agius, M. (2018) The use of Music Therapy in the treatment of Mental Illness and the enhancement of Societal Wellbeing. Psychiatria Danubina, 30(Suppl 7), 595–600.

Wang, S., Allen, D., Perkins, A., Monahan, P., Khan, S., Lasiter, S., Boustani, M., & Khan, B. (2019). Validation of a New Clinical Tool for Post-Intensive Care Syndrome. *American journal of critical care : an official publication, American Association of Critical-Care Nurses*, *28*(1), 10–18. https://doi.org/10.4037/ajcc2019639

Wang, Z., Neylan, T. C., Mueller, S. G., Lenoci, M., Truran, D., Marmar, C. R., Weiner, M. W., & Schuff, N. (2010) Magnetic resonance imaging of hippocampal subfields in posttraumatic stress disorder. Archives of General Psychiatry, 67(3), 296–303. https://doi.org/10.1001/archgenpsychiatry.2009.205

Warlan, H. (2016). Detection of Posttraumatic Stress Symptoms in Patients After Discharge from Intensive Care. *American Journal of Critical Care*, *25*(6), 509–515. https://doi /10.4037/ajcc2016573

Warner-Schmidt, J. L., & Duman, R. S. (2006) Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. Hippocampus, 16(3), 239–249. https://doi.org/10.1002/hipo.20156

Wassenaar, A., de Reus, J., Donders, A., Schoonhoven, L., Cremer, O. L., de Lange, D. W., van Dijk, D., Slooter, A., Pickkers, P., & van den Boogaard, M. (2018). Development and Validation of an Abbreviated Questionnaire to Easily Measure Cognitive Failure in ICU Survivors: A Multicenter Study. *Critical care medicine*, *46*(1), 79–84. https://doi.org/10.1097/CCM.0000000000002806

White, D. B., Angus, D. C., Shields, A. M., Buddadhumaruk, P., Pidro, C., Paner, C., Chaitin, E., Chang, C. H., Pike, F., Weissfeld, L., Kahn, J. M., Darby, J. M., Kowinsky, A., Martin, S., Arnold, R. M., & PARTNER Investigators (2018). A Randomized Trial of a Family-Support Intervention in Intensive Care Units. *The New England Journal of Medicine*, *378*(25), 2365–2375. https://doi.org/10.1056/NEJMoa1802637

Wild, J., & Gur, R. C. (2008). Verbal memory and treatment response in post-traumatic stress disorder. *The British journal of psychiatry : the journal of mental science*, *193*(3), 254–255. https://doi.org/10.1192/bjp.bp.107.045922

Williams, T., Phillips, N. J., Stein, D. J., & Ipser, J. C. (2022). Pharmacotherapy for post traumatic stress disorder (PTSD). *The Cochrane database of systematic reviews*, *3*(3), CD002795. https://doi.org/10.1002/14651858.CD002795.pub3

Wintermann, G. B., Rosendahl, J., Weidner, K., Strauß, B., Hinz, A., & Petrowski, K. (2018). Fatigue in chronically critically ill patients following intensive care - reliability and validity of the multidimensional fatigue inventory (MFI-20). *Health and quality of life outcomes*, *16*(1), 37. https://doi.org/10.1186/s12955-018-0862-6

Wintermann, G.-B., Brunkhorst, F. M., Petrowski, K., Strauss, B., Oehmichen, F., Pohl, M., & Rosendahl, J. (2015). Stress disorders following prolonged critical illness in survivors of severe sepsis. *Critical Care Medicine*, *43*(6), 1213–1222. https://doi.org/10.1097/CCM.0000000000000936

Xiong, K., Zhang, Y., Qiu, M., Zhang, J., Sang, L., Wang, L., Xie, B., Wang, J., & Li, M. (2013) Negative emotion regulation in patients with posttraumatic stress disorder. PloS one, 8(12), e81957. https://doi.org/10.1371/journal.pone.0081957

Xu, B., Sui, Y., Zhu, C., Yang, X., Zhou, J., Li, L., Ren, L., & Wang, X. (2017) Music intervention on cognitive dysfunction in healthy older adults: a systematic review and meta-analysis. Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 38(6), 983–992. https://doi.org/10.1007/s10072-017-2878-9

Yinger, O. S., & Gooding, L. F. (2015) A systematic review of music-based interventions for procedural support. *Journal of music therapy*, 52(1), 1–77. https://doi.org/10.1093/jmt/thv004

Yuan, C., Timmins, F., & Thompson, D. R. (2021). Post-intensive care syndrome: A concept analysis. *International Journal of nursing studies*, *114*, 103814. https://doi.org/10.1016/j.ijnurstu.2020.103814

Zante, B., Camenisch, S. A., & Schefold, J. C. (2020). Interventions in Post-Intensive Care Syndrome-Family: A Systematic Literature Review. *Critical care medicine*, *48*(9), e835–e840. https://doi.org/10.1097/CCM.0000000000004450

Zatorre R. J. (2015) Musical pleasure and reward: mechanisms and dysfunction. Annals of the New York Academy of Sciences, 1337, 202–211. https://doi.org/10.1111/nyas.12677

Zengin, N., Ören, B., & Üstündag, H. (2020) The relationship between stressors and intensive care unit experiences. Nursing in Critical Care, 25(2), 109–116. https://doi.org/10.1111/nicc.12465

Zergani, E. J., & Naderi, F. (2016) The Effectiveness of Music on Quality of Life and Anxiety Symptoms in the Post Traumatic Stress Disorder in Bustan Hospital of Ahvaz City. Review of European Studies, 8(3), 237–243. https://doi.org/10.5539/res.v8n3p237

Appendix S1

Table 1. Database searching: CINAHL via EBSCOhost (1946 to February 08, 2021)

Line number	Search terms	Number of results
S1	((checklist* OR questionnaire* OR survey* OR ((measure* OR scale* OR screening* OR psychometric* OR evaluat*) NEAR/3 (tool* OR assessment* OR index* OR indices))	803,653
S2	exp checklist/ or "surveys and questionnaires"/ or health care surveys/ or patient reported outcome measures/ or health surveys/ or patient health questionnaire/ or self report/	411,595
S3	S1 OR S2	866,196
S4	(("post intensive care" OR post-icu OR PICS))	1,301
S5	S3 AND S4	397
S6	(p?ediatric* or children or adolescen*)	26530
S7	S3 NOT S4	374

Table 2. Database searching: MEDLINE via Ovid (1946 to February 08, 2021)

Line number	Search terms	Number of results
1	exp checklist/ or "surveys and questionnaires"/ or health care surveys/ or patient reported outcome measures/ or health surveys/ or patient health questionnaire/ or self report/	595,959
2	(checklist* or questionnaire* or survey* or ((measure* or scale* or screening* or psychometric* or evaluat*) adj3 (tool* or assessment* or index* or indices))).mp.	1,463,818
3	1 or 2	1,481,837
4	("post intensive care" or Post-ICU or PICS).mp.	1,923
5	3 and 4	272
6	p?ediatric*.ti,ab.	368,709
7	5 not 6	260

Appendix S2

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Review

A Neurobiological Framework for the Therapeutic Potential of Music and Sound Interventions for Post-Traumatic Stress Symptoms in Critical Illness Survivors

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Abstract: Overview: Post traumatic stress disorder (PTSD) has emerged as a severely debilitating psychiatric disorder associated with critical illness. Little progress has been made in the treatment of post-intensive care unit (ICU) PTSD. Aim: To synthesize neurobiological evidence on the pathophysiology of PTSD and the brain areas involved, and to highlight the potential of music to treat post-ICU PTSD. Methods: Critical narrative review to elucidate an evidence-based neurobiological framework to inform the study of music interventions for PTSD post-ICU. Literature searches were performed in PubMed and CINAHL. The Scale for the Assessment of Narrative Review Articles (SANRA) guided reporting. Results: A dysfunctional HPA axis feedback loop, an increased amygdalic response, hippocampal atrophy, and a hypoactive prefrontal cortex contribute to PTSD symptoms. Playing or listening to music can stimulate neurogenesis and neuroplasticity, enhance brain recovery, and normalize stress response. Additionally, evidence supports effectiveness of music to improve coping and emotional regulation, decrease dissociation symptoms, reduce depression and anxiety levels, and overall reduce severity of PTSD symptoms. Conclusions: Despite the lack of music interventions for ICU survivors, music has the potential to help people suffering from PTSD by decreasing amygdala activity, improving hippocampal and prefrontal brain function, and balancing the HPA-axis.

Keywords: music; post traumatic stress disorder; critical illness; neurobiology; autonomic nervous system; limbic system

1. Introduction

Ongoing advancements in Intensive Care Unit (ICU) technology and evidence-based practice have significantly reduced ICU mortality. However, the intense stress and adverse emotions experienced during hospitalization in an ICU have long term effects on survivors' physiological and psychological well-being [1–3]. Post Traumatic Stress Disorder (PTSD) has emerged as a major long-term complication of critical illness, along with depression